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THE EFFECT OF MILK SUPPLEMENTS ON THE GROWTH OF CHILDREN WITH NUTRITIVE FAILURE

THE WETZEL GRID FINDINGS

TOM D. SPIES, M.D., AND SAMUEL DREIZEN, D.D.S.
BIRMINGHAM, ALA.

FROM the moment of conception to the attainment of physical maturity, the growth of a person is characterized by an increase in size and an increase in cell complexity. Under optimum conditions the growth process is distinguished by a high degree of orderliness and stability. Growth may be thought of as the summation of the functions of a number of fundamental biochemical systems, any of which may be easily affected by a large variety of exogenous and endogenous factors. Prominent among these factors is a diet deficient in essential nutrients.

The effects of chronic malnutrition on the growth progress of children born to parents with long-standing nutritive failure in a region of endemic nutritional deficiency diseases have been studied at the Nutrition Clinic of the Hillman Hospital, Birmingham, Ala., since 1936. It has been observed and reported that, in general, the growth progress of such children is irregular, unstable, and retarded.[1, 2] Physically, the children are somewhat smaller and leaner than adequately nourished children of the same age group and racial stock.[1] Although specific nutritional deficiency lesions are seldom seen in infancy in children with chronic nutritive failure, they frequently appear early in childhood and show a pronounced tendency to recur in the late spring and summer when the incidence of retarded growth in this group is most common.[3, 4, 5]

Although the health of a child and his status as an adult cannot be measured in terms of size alone, prolonged failure to grow is extremely important, as every child must liquidate his growth debt by the time the epiphyses and diaphyses of the major long bones have fused; otherwise, he can never attain the maximum physical development dictated by his own growth pattern. In 1945, a special three-year study was initiated to determine the effect of the daily supplementation of a known amount of either whole or nonfat dried milk on the growth progress of a selected group of children with chronic nutritive failure. Three different methods, namely, analyses of roentgenograms of the hand, wrist, and forearm, photographs in the nude, and

Northwestern University Studies in Nutrition at the Hillman Hospital, Birmingham. From the Department of Nutrition and Metabolism, Northwestern University.

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the Wetzel Grid were used singly and in conjunction, to measure the changes in growth which occurred in each child during the period of investigation.[2] The present report is confined to the Wetzel Grid findings.

MATERIALS AND METHODS

Selection of Patients.—The eighty-two subjects included in this study were selected from more than 300 children who were patients of the Nutrition Clinic. The preliminary selection was made on the basis of: (a) history or evidence of nutritive failure in the child, parents, or older siblings; (b) chronological age; (c) freedom from contagious or infectious disease and allergy to cows milk; and (d) accessibility of the home and the cooperative attitude of the parents.

After considering the roentgenographic and height-weight data of each of the children who met the preliminary requirements, forty-one pairs of children were chosen for this investigation. The forty-one pairs included twenty-three pairs of girls and eighteen pairs of boys, ranging in age from 4 to 15 years. All of the subjects were white, of Anglo-Saxon extraction, and, for the most part, natives of north-central Alabama. The criteria for the pairings were: (a) sex; (b) comparative roentgenograms of the left hand, wrist, and forearm; (c) general body type; and (d) the apparent prevailing phase of growth.

Method of Study.—The period of study comprised three different phases: namely, (a) a premilk phase of several years' duration in which the data used in the selection of some of the children were collected and the methods subsequently used to measure growth progress introduced, tested and, evaluated; (b) a milk phase, which began in April, 1945, and extended for twenty months (during this time one child in each pair was given a supplement of the equivalent of one quart of milk each day, six days a week); and (c) a postmilk phase, which began immediately after the discontinuation of the milk supplement and extended for twelve months. The findings reported in this paper cover only the milk and postmilk phases, the two periods in which all of the selected children were subjected to arbitrarily fixed standard procedures based on the experience obtained during the premilk phase.

The supplement for one child in each pair consisted of either 3 ounces of nonfat milk powder or 4¼ ounces of whole milk powder. The additional 1¼ ounces of whole milk solids were given in order to keep the protein content of the two types of supplement approximately the same. Twenty-two children (nine boys and thirteen girls) received the nonfat milk, while nineteen (nine boys and ten girls) received the whole milk. The milk powder was mixed with water by an electric churn under aseptic conditions, and in most instances brought up to one pint volume (approximately 500 c.c.) by clinic personnel under the direction of Miss Jean Grant and Miss Catherine Sims. To facilitate intake, the final volume in some cases consisted of one-half pint (approximately 250 c.c.), but in no instance was the amount of milk

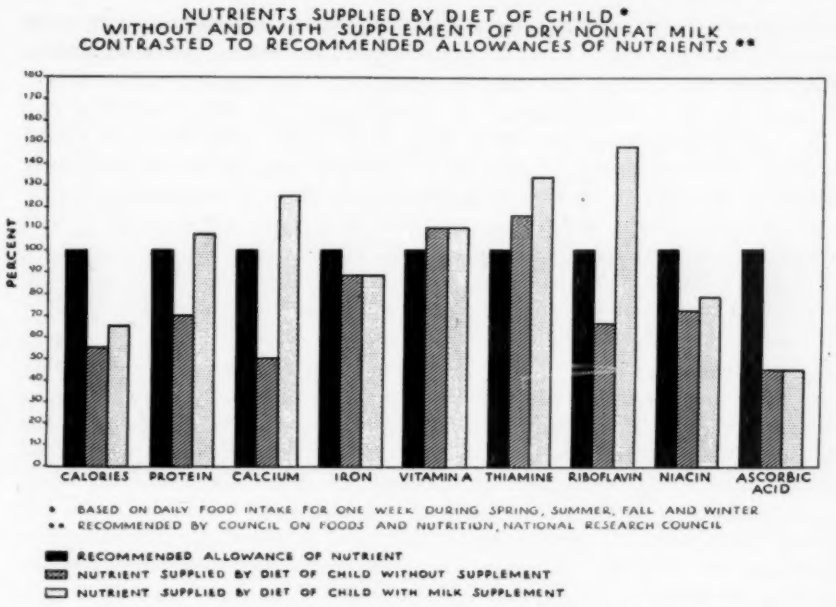
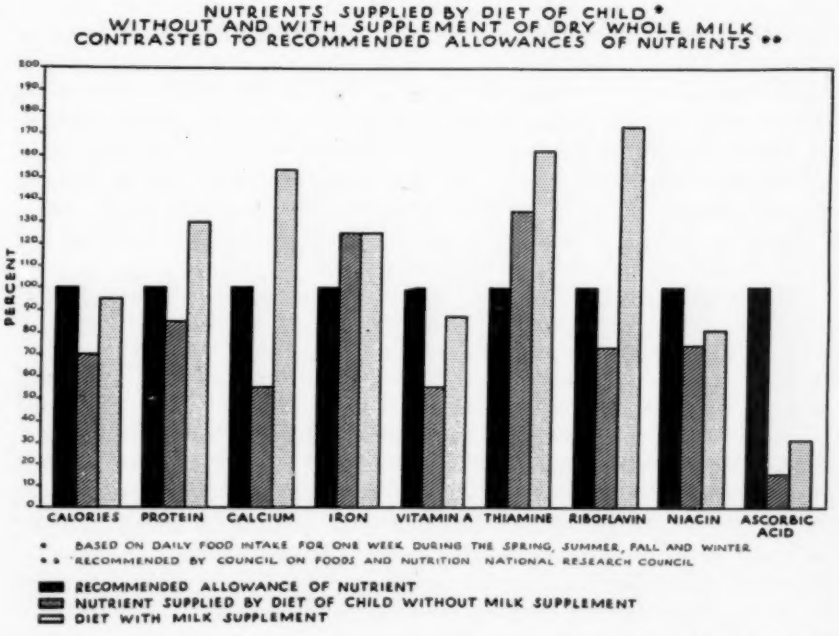

NUTRIENTS SUPPLIED BY DIET OF CHILD *
WITHOUT AND WITH SUPPLEMENT OF DRY NONFAT MILK
CONTRASTED TO RECOMMENDED ALLOWANCES OF NUTRIENTS **
PERCENT
CALORIES
PROTEIN
CALCIUM
IRON
VITAMIN A
THIAMINE
RIBOFLAVIN
NIACIN
ASCORBIC ACID
* BASED ON DAILY FOOD INTAKE FOR ONE WEEK DURING SPRING, SUMMER, FALL AND WINTER
** RECOMMENDED BY COUNCIL ON FOODS AND NUTRITION, NATIONAL RESEARCH COUNCIL
RECOMMENDED ALLOWANCE OF NUTRIENT
NUTRIENT SUPPLIED BY DIET OF CHILD WITHOUT SUPPLEMENT
NUTRIENT SUPPLIED BY DIET OF CHILD WITH MILK SUPPLEMENT

Fig. 1.—A representative diet of a child in the test group with and without the nonfat milk supplement.


NUTRIENTS SUPPLIED BY DIET OF CHILD *
WITHOUT AND WITH SUPPLEMENT OF DRY WHOLE MILK
CONTRASTED TO RECOMMENDED ALLOWANCES OF NUTRIENTS **
PERCENT
CALORIES
PROTEIN
CALCIUM
IRON
VITAMIN A
THIAMINE
RIBOFLAVIN
NIACIN
ASCORBIC ACID
* BASED ON DAILY FOOD INTAKE FOR ONE WEEK DURING THE SPRING, SUMMER, FALL AND WINTER
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RECOMMENDED ALLOWANCE OF NUTRIENT
NUTRIENT SUPPLIED BY DIET OF CHILD WITHOUT MILK SUPPLEMENT
DIET WITH MILK SUPPLEMENT

Fig. 2.—A representative diet of a child in the test group with and without the whole milk supplement.

solids given per day reduced. The suspended milk was placed in a refrigerator overnight and personally given to the children the next day by Miss Martha Hutchinson, Mrs. Nelwyn Dill, Miss Catherine Sims, Miss Verna Lee Moore, Mrs. Merle Babb, Mrs. Martha Nez, Miss Jerome Kennedy, Miss Jo Gilley, and Mrs. Mabel Morey, social service workers on the staff of the Nutrition Clinic. Each worker was assigned a number of children and had the responsibility of getting the milk to these children and seeing that the supplement was ingested by each child. When the supplement was refused in whole or in part at any time for any reason, it was returned to the clinic and the amount refused was noted on a record kept for each child. The effect of the milk supplement on the nutritive value of representative diets of two of the children included in the study are shown in Figs. 1 and 2.

No attempt was made to alter the habits of the children in any way other than by giving them the milk as a supplement to their daily dietaries. Any voluntary changes in the living conditions, habits, or dietaries of any of the children which occurred during either the milk or postmilk phase were noted and reported by the social service workers. In order to estimate the effect of the supplement or lack of it on the growth progress of each child, the following principles of therapy were applied: (a) symptomatic treatment and treatment for coexisting diseases other than nutritional deficiency diseases were given when indicated; (b) no nutritional therapy or dietary supplements other than milk were prescribed or added; and (c) conditions causing excessive requirements for the various nutrients were analyzed wherever possible.

Each child was brought to the clinic for examination for evidence of nutritive failure at least once every two months. A complete physical examination was made on each child once each year by Dr. Esther Gross. The children were weighed and measured at each of these examinations. Height was obtained by use of the Baldwin Paper Measuring Scale.[6] The shoes were removed and each child's height was taken in the standing position with the feet together and the heels, buttocks, shoulders, and head touching the scale. Weight was obtained with a Continental scale, the children being required to remove their shoes and outer clothing before being weighed.

The height-weight data for each child were plotted on individual Wetzel Grids.[7] Recently the originator of the Wetzel Grid published a treatise in which may be found many of the technical details for evaluating physical fitness in terms of physique (body build), developmental level, and basal metabolism.[8] Only those salient features of the Grid technique which formed the basis for the analysis of the Grid data included in this study are presented in the following paragraph.

According to the interpretation of the authors, in the Grid technique the quality of a child's growth is determined from an analysis of the direction and speed of his development.[8] The direction of development is denoted by the child's position in the channel system as plotted from successive points and compared to the direction of the channel system itself. The speed of

development is indicated by the position of the child in the auxodrome panel, plotted from successive points and related to the standard age schedules of development. Growth to be acceptable in quality, should not deviate beyond stated limits of tolerance either in direction or speed from the pattern set by the channel system or standard auxodromes. The limits of tolerance are a shift of one-half channel per ten levels of advancement and a deviation of not more than two to three levels per year from the expected schedule.[9] By the Grid technique, therefore, the objective signs of failing growth consist of: (a) developmental lag or the failure of the child to keep up with his expected age schedule of development, and (b) loss of physique characterized by a shift in the channel curve to the lower outer border of the channel system.[10]

OBSERVATIONS

For ease of presentation, the findings derived from the Wetzel Grid data for each child during both the milk and postmilk phases of the study are listed under five aspects of growth progress, each of which was evaluated by the Grid technique. These include: (a) direction of development, (b) speed of development, (c) rate of development,* (d) quality of growth, and (e) incidence of episodes of growth failure.

THE EFFECT OF THE MILK SUPPLEMENTS ON THE DIRECTION OF DEVELOPMENT (WETZEL)

The Milk Period.—The changes in the direction of development of the test and control groups of children during the twenty-month period in which they received the milk supplements are shown in Figs. 3 and 4. It will be noted that in fourteen (34 per cent) of the children who received the milk supplements, the direction of development improved, while in nine (22 per cent) there was no change, and eighteen (44 per cent) drifted to the right and down, indicating a loss of physique. In the same period the physique improved in six (15 per cent) of the children in the control group, there was no change in eleven (27 per cent), and there was a loss of status in twenty-four (59 per cent). A summary of these findings is shown in Table I. Improvement in direction of development during this period was most frequent among the girls receiving the nonfat milk, followed in incidence by the boys receiving the whole milk, the girls receiving the whole milk, the girls in the control group, the boys receiving the nonfat milk, and the boys in the control group.

The Postmilk Period.—The changes in the direction of development which occurred among both groups of children during the twelve-month postsupplementation period are included in Figs. 3 and 4. In ten (24 per cent) of the children in the test group the physique rating improved, in sixteen (39 per

*The rate of the 67 per cent auxodrome (i.e., the speed of progress called for by that auxodrome at successive ages) is approximately one level line per month throughout its entire range. The rate of every other auxodrome is also approximately one level per month over the same range. The rate of development is, therefore, independent of auxodrome from 5 years of age and up and is approximately the same for children on any and all auxodromes.[11]

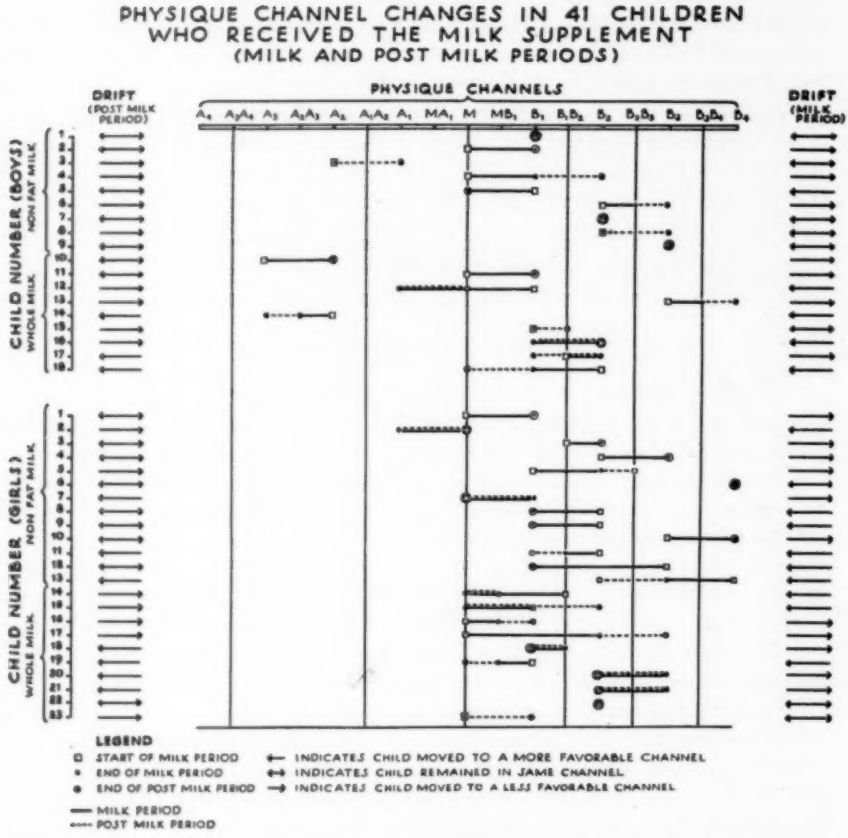


Fig. 3.—The changes in direction of development in the children receiving the milk supplements during the milk and postmilk periods.

cent) it did not change, whereas fifteen (37 per cent) moved into less favorable channels. The corresponding values for the children in the control group were seven (17.5 per cent), seventeen (42.5 per cent), and sixteen (40 per cent). One of the children in the control group did not return for examination during this phase, and is, therefore, not included in this tabulation. The findings of the postmilk period are summarized in Table II. The most extensive improvement in direction of development during this period occurred in the girls who had received the whole milk, followed in frequency by the boys who had received the whole milk, the girls who had received the nonfat milk, the girls in the control group, the boys in the control group, and the boys who had received the nonfat milk.

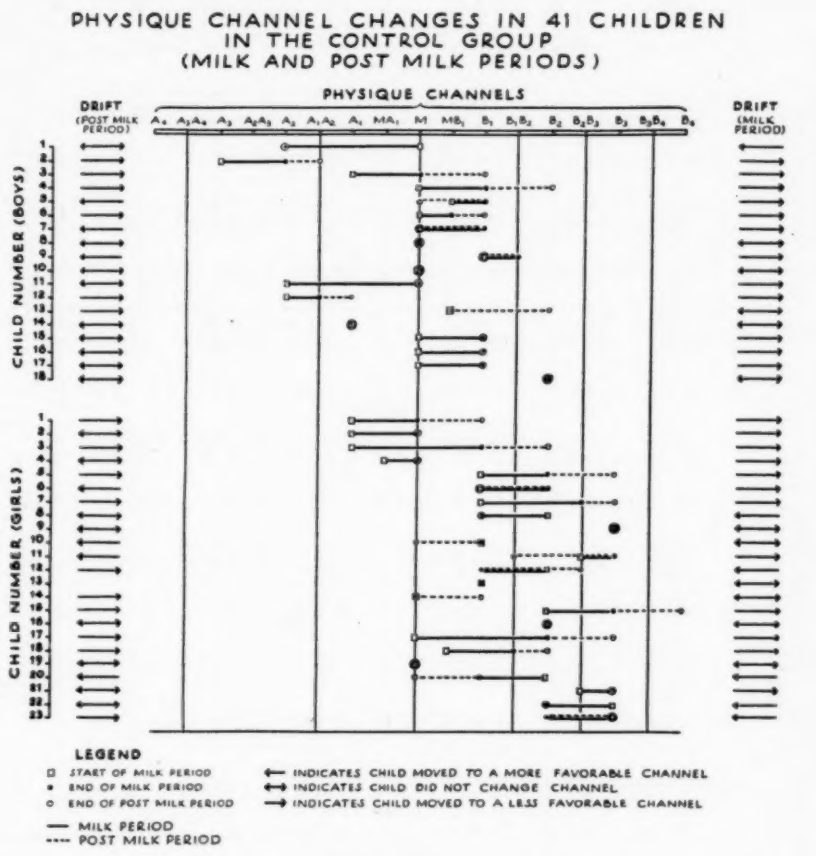

PHYSIQUE CHANNEL CHANGES IN 41 CHILDREN
IN THE CONTROL GROUP
(MILK AND POST MILK PERIODS)
PHYSIQUE CHANNELS
DRIFT (POST MILK PERIOD)
DRIFT (MILK PERIOD)
CHILD NUMBER (BOYS)
CHILD NUMBER (GIRLS)
LEGEND
START OF MILK PERIOD
END OF MILK PERIOD
END OF POST MILK PERIOD
MILK PERIOD
POST MILK PERIOD
INDICATES CHILD MOVED TO A MORE FAVORABLE CHANNEL
INDICATES CHILD DID NOT CHANGE CHANNEL
INDICATES CHILD MOVED TO A LESS FAVORABLE CHANNEL

Fig. 4.—The changes in direction of development in the children in the control group during the milk and postmilk periods.

Five of the fourteen children in the test group who had bettered their direction of development during the milk period continued to improve in this respect throughout the postmilk phase of the study. Direction was maintained in four of the fourteen children, while in five there was a loss of status. Of the six children in the control group in whom improvement in the direction of development occurred during the supplementation period, one continued to improve, three maintained their direction, and two moved to less favorable channels in the postmilk period (Table III).

TABLE I. CHANGES IN GROWTH AS DETERMINED FROM THE WETZEL GRID IN FORTY-ONE TEST AND FORTY-ONE CONTROL CHILDREN DURING THE TWENTY-MONTH PERIOD OF MILK SUPPLEMENTATION

TYPE OF CHANGE	TEST CASES										CONTROL CASES					
	WHOLE MILK				NONFAT MILK											
	BOYS		GIRLS		BOYS		GIRLS		TOTAL		BOYS		GIRLS		TOTAL	
	NO.	%	NO.	%	NO.	%	NO.	%	NO.	%	NO.	%	NO.	%	NO.	%
Channel Changes: (Direction of Development)																
More favorable position	4	44.4	3	30.0	1	11.1	6	46.2	14	34.1	1	5.5	5	21.7	6	14.6
Position unchanged	1	11.1	2	20.0	5	55.5	1	7.7	9	22.0	5	27.8	6	26.1	11	26.8
Less favorable position	4	44.4	5	50.0	3	33.3	6	46.2	18	43.9	12	66.7	12	52.2	24	58.5
Changes in Auxodrome: (Speed of Development)																
Faster auxodrome	8	88.9	4	40.0	2	27.2	8	61.6	22	53.6	1	5.5	2	8.7	3	7.3
Auxodrome unchanged	0	00.0	1	10.0	1	11.1	0	00.0	2	4.9	1	5.5	3	13.0	4	9.8
Slower auxodrome	1	11.1	5	50.0	6	66.6	5	38.4	17	41.5	16	88.9	18	78.3	34	82.9
Changes in Levels per Month: (Rate of Development)																
More than one level per month	8	88.9	8	80.0	5	55.5	9	69.2	30	73.2	8	44.4	8	34.8	16	39.0
Exactly one level per month	1	11.1	0	00.0	0	00.0	1	7.7	2	4.9	0	00.0	0	00.0	0	00.0
Less than one level per month	0	00.0	2	20.0	4	44.4	3	23.1	9	22.0	10	55.5	15	65.2	25	61.0
Changes in Growth Quality: (Speed and Direction of Development)																
More favorable channel; faster schedule	4	44.4	3	30.0	0	00.0	4	30.8	11	26.8	0	00.0	0	00.0	0	00.0
More favorable channel; schedule unchanged	0	11.1	0	20.0	0	11.1	0	7.7	0	12.2	0	5.6	1	8.7	1	7.3
Channel unchanged; faster schedule	1		2		1		1		5		1		1		2	
Channel unchanged; schedule unchanged	0	00.0	0	00.0	0	00.0	0	00.0	0	00.0	1	5.6	0	00.0	1	2.4
More favorable channel; slower schedule	0	33.3	0	00.0	1	22.2	2	46.2	3	26.8	1	5.6	4	21.7	5	14.6
Less favorable channel; faster schedule	3		0		1		4		8		0		1		1	
Channel unchanged; slower schedule	0	00.0	0	00.0	4	55.5	0	00.0	4	12.2	3	16.7	5	30.4	8	24.4
Less favorable channel; schedule unchanged	0		0		1		0		1		0		2		2	
Less favorable channel; slower schedule	1	11.1	5	50.0	1	11.1	2	15.4	9	21.9	12	66.7	9	39.1	21	51.2
Number of Instances of Growth Failure: (Simultaneous Loss in Speed and Direction of Development)																
0	5	55.5	3	30.0	1	11.1	2	15.4	11	26.8	3	16.7	5	21.7	8	19.5
1	2	22.2	5	50.0	2	22.2	5	38.5	14	34.1	8	44.4	5	21.7	13	31.7
2	1	11.1	2	20.0	3	33.3	5	38.5	11	26.8	5	27.8	13	56.5	18	43.9
3	1	11.1	0	00.0	2	22.2	1	7.7	4	9.8	2	11.1	0	00.0	2	4.9
4	0	00.0	0	00.0	1	11.1	0	00.0	1	2.4	0	00.0	0	00.0	0	00.0

TABLE II. CHANGES IN GROWTH AS DETERMINED FROM THE WETZEL GRID IN FORTY-ONE TEST AND FORTY CONTROL CHILDREN DURING THE TWELVE-MONTH POSTSUPPLEMENTATION PERIOD

1	2	22.2	5	50.0	2	22.2	5	38.5	14	34.1	8	44.4	5	21.7	13	31.7
2	1	11.1	2	20.0	3	33.3	5	38.5	11	26.8	5	27.8	13	56.5	18	43.9
3	1	11.1	0	00.0	2	22.2	1	7.7	4	9.8	2	11.1	0	00.0	2	4.9
4	0	00.0	0	00.0	1	11.1	0	00.0	1	2.4	0	00.0	0	00.0	0	00.0

TABLE II. CHANGES IN GROWTH AS DETERMINED FROM THE WETZEL GRID IN FORTY-ONE TEST AND FORTY CONTROL CHILDREN DURING THE TWELVE-MONTH POSTSUPPLEMENTATION PERIOD

	TEST CASES										CONTROL CASES					
	WHOLE MILK				NONFAT MILK											
	BOYS		GIRLS		BOYS		GIRLS		TOTAL		BOYS		GIRLS		TOTAL	
TYPE OF CHANGE	NO.	%	NO.	%	NO.	%	NO.	%	NO.	%	NO.	%	NO.	%	NO.	%
Channel Changes: (Direction of Development)																
More favorable position	3	33.3	4	40.0	0	00.0	3	23.1	10	24.4	3	16.6	4	18.2	7	17.5
Position unchanged	2	22.2	1	10.0	5	55.5	8	61.5	16	39.0	9	50.0	8	36.4	17	42.5
Less favorable position	4	44.4	5	50.0	4	44.4	2	15.4	15	36.6	6	33.3	10	45.4	16	40.0
Changes in Auxodrome: (Speed of Development)																
Faster auxodrome	3	33.3	3	30.0	1	11.1	2	15.4	9	22.0	3	16.6	2	9.1	5	12.5
Auxodrome unchanged	1	11.1	2	20.0	0	00.0	3	23.1	6	14.6	3	16.6	2	9.1	5	12.5
Slower auxodrome	5	55.5	5	50.0	8	88.9	8	61.5	26	63.4	12	66.7	18	81.8	30	75.0
Changes in Levels per Month: (Rate of Development)																
More than one level per month	3	33.3	2	20.0	2	22.2	4	30.8	10	24.4	4	22.2	8	36.4	12	30.0
Exactly one level per month	0	00.0	2	20.0	0	00.0	2	15.4	4	9.8	2	11.1	1	4.5	3	7.5
Less than one level per month	6	66.7	6	60.0	7	77.8	7	63.8	27	65.9	12	66.7	13	59.1	25	62.5
Changes in Growth Quality: (Speed and Direction of Development)																
More favorable channel; faster schedule	3	33.3	2	20.0	0	00.0	1	7.7	6	14.6	2	11.1	1	4.5	3	7.5
More favorable channel; schedule unchanged	0	00.0	2	30.0	0	00.0	1	15.4	3	12.2	0	5.5	1	9.1	1	7.5
Channel unchanged; faster schedule	0		1		0		1		2		1		1		2	
Channel unchanged; schedule unchanged	0	00.0	0	00.0	0	00.0	1	7.7	1	2.4	3	16.6	1	4.5	4	10.0
More favorable channel; slower schedule	0	00.0	0	00.0	0	11.1	1	7.7	1	4.8	1	5.5	2	9.1	3	7.5
Less favorable channel; faster schedule	0		0		1		0		1		0		0		0	
Channel unchanged; slower schedule	3	33.3	0	00.0	4	55.5	6	53.8	13	36.6	5	27.8	6	27.3	11	27.5
Less favorable channel; schedule unchanged	0		0		1		1		2		0		0		0	
Less favorable channel; slower schedule	3	33.3	5	50.0	3	33.3	1	7.7	12	29.3	6	33.3	10	45.4	16	40.0
Number of Instances of Growth Failure: (Simultaneous Loss in Speed and Direction of Development)																
0	3	33.3	1	10.0	1	11.1	4	30.8	9	22.0	9	50.0	7	31.8	16	40.0
1	3	33.3	7	70.0	6	66.7	8	61.5	24	58.5	5	27.8	12	54.5	17	42.5
3	2	22.2	2	20.0	2	22.2	1	7.7	7	17.1	3	16.6	2	9.1	5	12.5
2	1	11.1	0	00.0	0	00.0	0	00.0	1	2.4	1	5.5	1	4.5	2	5.0

TABLE III. THE CHANGES IN THE DIRECTION, SPEED, AND RATE OF DEVELOPMENT IN FORTY-ONE TEST AND FORTY-ONE CONTROL CHILDREN DURING THE MILK AND POSTMILK PHASES OF THE STUDY*

TYPE OF CHANGE	TEST CASES										CONTROL CASES					
	WHOLE MILK				NONFAT MILK				TOTAL		BOYS		GIRLS		TOTAL	
	BOYS		GIRLS		BOYS		GIRLS									
	NO.	%	NO.	%	NO.	%	NO.	%	NO.	%	NO.	%	NO.	%	NO.	%
Channel Changes: (Direction of Development)																
Milk Phase:† Postmilk Phase:																
← ←	2	22.2	1	10.0	0	00.0	2	15.4	5	12.2	0	00.0	1	4.5	1	2.5
← ↔	0	00.0	0	00.0	1	11.1	3	23.0	4	9.8	1	5.6	2	9.1	3	7.5
← →	1	11.1	2	20.0	1	11.1	1	7.7	5	12.2	0	00.0	2	9.1	2	5.0
↔ ↔	0	00.0	1	10.0	3	33.3	1	7.7	5	12.2	4	22.2	3	13.6	7	17.5
↔ →	1	11.1	1	10.0	2	22.2	0	00.0	4	9.8	1	5.6	1	4.5	2	5.0
↔ ←	0	00.0	0	00.0	0	00.0	0	00.0	0	00.0	0	00.0	1	4.5	1	2.5
→ →	2	22.2	2	20.0	1	11.1	1	7.7	6	14.6	5	27.7	7	31.8	12	30.0
→ ↔	2	22.2	0	00.0	1	11.1	4	30.7	7	17.0	4	22.2	3	13.6	7	17.5
→ ←	1	11.1	3	30.0	0	00.0	1	7.7	5	12.2	3	16.7	2	9.1	5	12.5
Changes in Auxodrome: (Speed of Development)																
Milk Phase:‡ Postmilk Phase:																
← ←	3	33.3	1	10.0	0	00.0	2	15.4	6	14.6	1	5.6	1	4.5	2	5.0
← ↔	1	11.1	0	00.0	0	00.0	3	23.0	4	9.8	0	00.0	0	00.0	0	00.0
← →	4	44.4	3	30.0	2	22.2	3	23.0	12	29.3	0	00.0	1	4.5	1	2.5
↔ ↔	0	00.0	0	00.0	0	00.0	0	00.0	0	00.0	0	00.0	0	00.0	0	00.0
↔ →	0	00.0	0	00.0	1	11.1	0	00.0	1	2.4	1	5.6	3	13.6	4	10.0
↔ ←	0	00.0	1	10.0	0	00.0	0	00.0	1	2.4	0	00.0	0	00.0	0	00.0
→ →	1	11.1	2	20.0	5	55.5	5	38.5	13	31.7	11	61.1	13	59.1	24	60.0
→ ↔	0	00.0	2	20.0	0	00.0	0	00.0	2	4.9	3	16.7	3	13.6	6	15.0
→ ←	0	00.0	1	10.0	1	11.1	0	00.0	2	4.9	2	11.1	1	4.5	3	7.5
Changes in Levels per Month: (Rate of Development)																
Milk Phase:§ Postmilk Phase:																
← ←	3	33.3	1	10.0	1	11.1	3	23.0	8	19.5	1	5.6	3	13.6	4	10.0
← ↔	0	00.0	2	20.0	0	00.0	1	7.7	3	7.3	1	5.6	0	00.0	1	2.5
← →	5	55.5	5	50.0	4	44.4	5	38.5	19	46.3	6	33.3	5	22.7	11	27.5
↔ ↔	0	00.0	0	00.0	0	00.0	0	00.0	0	00.0	0	00.0	0	00.0	0	00.0
↔ →	1	11.1	0	00.0	0	00.0	1	7.7	2	4.9	0	00.0	0	00.0	0	00.0
↔ ←	0	00.0	0	00.0	0	00.0	0	00.0	0	00.0	0	00.0	0	00.0	0	00.0
→ →	0	00.0	2	20.0	3	33.3	1	7.7	6	14.6	6	33.3	8	36.4	14	35.0
→ ↔	0	00.0	0	00.0	0	00.0	1	7.7	1	2.4	1	5.6	1	4.6	2	5.0
→ ←	0	00.0	0	00.0	1	11.1	1	7.7	2	4.9	3	16.7	5	22.7	8	20.0

*One of the control children did not return for examination during the postmilk phase and, therefore, is not included in the postmilk data.

†← More favorable channel.
↔ Channel unchanged.
→ Less favorable channel.

‡← Faster auxodrome.
↔ Auxodrome unchanged.
→ Slower auxodrome.

§← Made more than one level per month.
↔ Made exactly one level per month.
→ Made less than one level per month.

THE EFFECT OF THE MILK SUPPLEMENTS ON THE SPEED OF DEVELOPMENT (WETZEL)

The Milk Period.—The changes in the speed of development which occurred among the children in the test and control groups during this phase of the study are shown in Figs. 5 and 6. Twenty-two (54 per cent) of the children receiving the supplements moved to faster schedules, two (5 per cent) did not change, and seventeen (41.5 per cent) moved to slower schedules. In contrast, three (7 per cent) of the children in the control group moved to

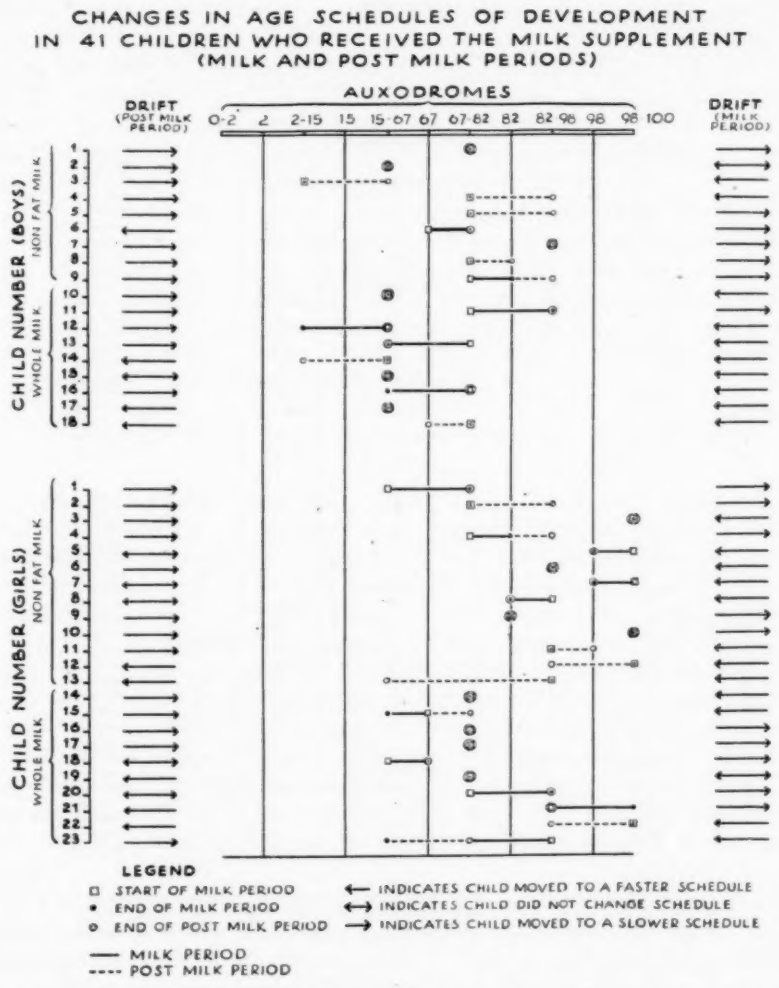

CHANGES IN AGE SCHEDULES OF DEVELOPMENT
IN 41 CHILDREN WHO RECEIVED THE MILK SUPPLEMENT
(MILK AND POST MILK PERIODS)
AUXODROMES
DRIFT (POST MILK PERIOD)
0-2 2 2-15 15 15-67 67 67-82 82 82-98 98 98-100
DRIFT (MILK PERIOD)
CHILD NUMBER (BOYS)
WHOLE MILK
NON FAT MILK
CHILD NUMBER (GIRLS)
WHOLE MILK
NON FAT MILK
LEGEND
START OF MILK PERIOD
END OF MILK PERIOD
END OF POST MILK PERIOD
MILK PERIOD
POST MILK PERIOD
INDICATES CHILD MOVED TO A FASTER SCHEDULE
INDICATES CHILD DID NOT CHANGE SCHEDULE
INDICATES CHILD MOVED TO A SLOWER SCHEDULE

Fig. 5.—The changes in speed of development in the children receiving the milk supplements during the milk and postmilk periods.

faster schedules, four (10 per cent) did not change, and thirty-four (83 per cent) moved to slower schedules. This occurred despite the observation that most of the children in the control group were on slow age schedules of development at the beginning of the study (Fig. 6). The sex differences and the differences observed in the children receiving the whole and nonfat milk are shown in Table I. Improvement in the speed of development was most frequent among the boys who received the whole milk supplement, followed in incidence by the girls who received the nonfat milk, the girls who received the whole milk, the boys who received the nonfat milk, the girls in the control group, and the boys in the control group.

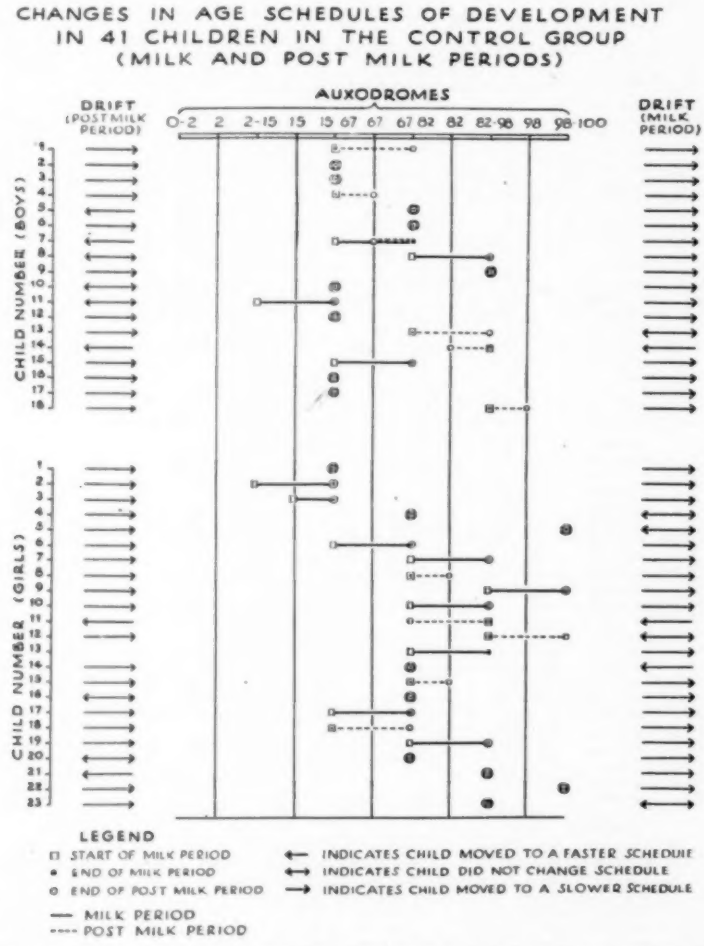

CHANGES IN AGE SCHEDULES OF DEVELOPMENT
IN 41 CHILDREN IN THE CONTROL GROUP
(MILK AND POST MILK PERIODS)
AUXODROMES
DRIFT (POST MILK PERIOD)
DRIFT (MILK PERIOD)
0-2 2 2-15 15 15 67 67 67 82 82 82-98 98 98 100
CHILD NUMBER (BOYS)
CHILD NUMBER (GIRLS)
LEGEND
START OF MILK PERIOD
END OF MILK PERIOD
END OF POST MILK PERIOD
MILK PERIOD
POST MILK PERIOD
INDICATES CHILD MOVED TO A FASTER SCHEDULE
INDICATES CHILD DID NOT CHANGE SCHEDULE
INDICATES CHILD MOVED TO A SLOWER SCHEDULE

Fig. 6.—The changes in the speed of development in the children in the control group during the milk and postmilk periods.

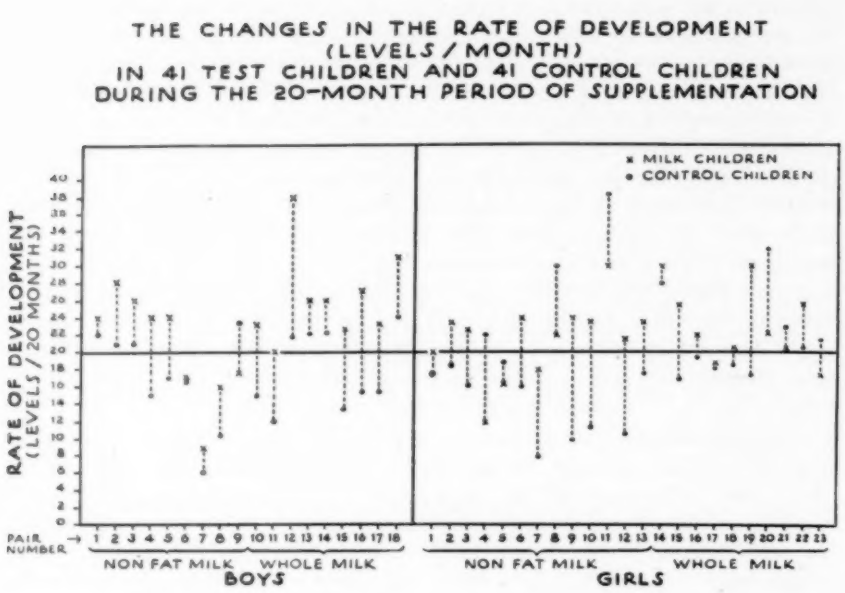
The Postmilk Period.—Figs. 5 and 6 show the findings relative to the changes in the speed of development which occurred in the children in the test group and in the children in the control group during the twelve-month postsupplementation period. Nine (22 per cent) of the children receiving the supplement moved to faster age schedules of development, six (15 per cent) did not change, and twenty-six (63 per cent) drifted to slower schedules. Among the children in the control group the schedules improved in five (12.5 per cent), five (12.5 per cent) did not change, and thirty (75 per cent) moved to slower schedules. These findings are summarized in Table II on the basis of the sex of the child and the type of milk supplement received during the first phase of the study. Improvement in the speed of development was most prevalent among the boys who had received the whole milk supplement, followed in frequency by the girls who had received the whole milk supplement, the boys in the control group, the girls who had received the nonfat milk, the boys who had received the nonfat milk, and the girls in the control group.

Only six of the twenty-two children in the test group who improved their speed of development during the milk period continued to improve following the withdrawal of the supplement. Four maintained their faster schedules, while twelve moved to slower schedules. Of the three children in the control group whose speed of development improved during the milk period, two continued to shift to faster schedules, while one moved to a slower schedule during the postmilk period (Table III).

THE EFFECT OF THE MILK SUPPLEMENTS ON THE RATE OF DEVELOPMENT (WETZEL)

The Milk Period.—A summary of the rate of development of the children in the test and control groups during the twenty-month period of supplementation is shown in Fig. 7. Thirty (73 per cent) of the children in the test group proceeded at the rate of more than one level per month during this phase, while two (5 per cent) made exactly one level per month, and nine (22 per cent) progressed at a rate of less than one level per month. In contrast, only sixteen (39 per cent) of the children in the control group made more than one level per month, and twenty-five (61 per cent) made less than one level per month. On the basis of sex of the child and type of milk ingested (Table I) improvement in rate occurred most frequently among the boys receiving the whole milk, followed in descending order by the girls receiving the whole milk, the girls receiving the nonfat milk, the boys receiving the nonfat milk, the boys in the control group, and the girls in the control group.

The Postmilk Period.—The changes in the rate of development which occurred in the children in the test and in the control groups during the twelve-month postmilk period are shown in Fig. 7. Ten (24 per cent) of the children in the test group progressed at the rate of more than one level per month, four (10 per cent) made exactly one level per month, and twenty-seven (66 per



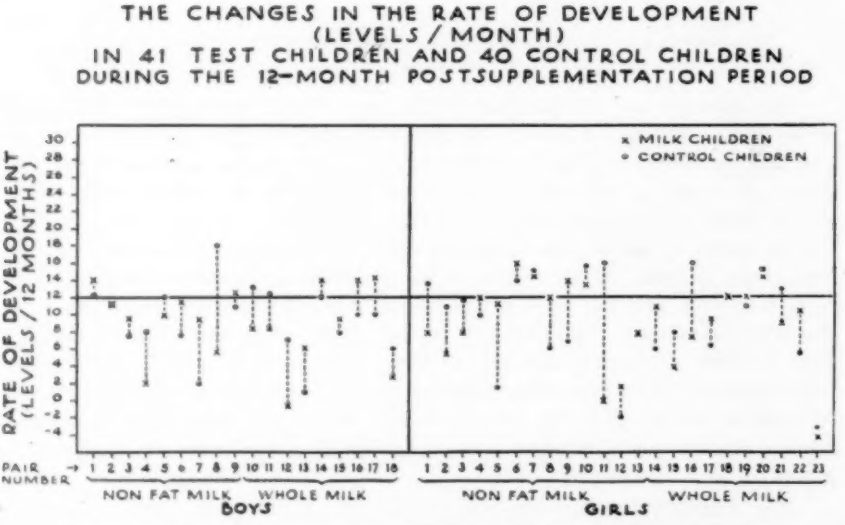


Fig. 7.—The changes in the rate of development (levels per month) in the children receiving the milk supplements and in the children in the control group during the milk and postmilk periods.

cent) made less than one level per month. Twelve (30 per cent) of the children in the control group made more than one level per month, three (7.5 per cent) made exactly one level per month, and twenty-five (62.5 per cent) made less than one level per month during this phase of the study. Table II shows a summary of these findings. Improvement was most prevalent among the girls in the control group, followed in frequency by the boys who had received the whole milk supplement, the girls who had received the nonfat milk supplement, the boys who had received the nonfat milk supplement, the boys in the control group, and the girls who had received the whole milk supplement.

Of the thirty children in the test group who made more than one level per month during the milk period, eight continued to make more than one level per month, three made exactly one level per month and nineteen made less than one level per month after the supplement was discontinued. By comparison, four of the sixteen children in the control group who made more than one level per month during the milk period, continued at the rate of more than one level per month, one made exactly one level per month, while eleven made less than one level per month during the postmilk phase of the study (Table III).

THE EFFECT OF THE MILK SUPPLEMENTS ON THE QUALITY OF GROWTH (WETZEL)

The Milk Period.—The changes in the quality of growth in the individual children in the test and control groups during the supplementation phase of the study are shown in Table I. In eleven (27 per cent) of the children receiving the supplements the quality of growth improved in both of its components (speed of development and direction of development); five (12 per cent) improved in one component while maintaining their position in the other; eleven (27 per cent) improved in one component but underwent undesirable changes in the second; five (12 per cent) underwent a detrimental change in one component while the second remained unchanged; and nine (22 per cent) failed to maintain both their speed and direction of development, a factor suggestive of poor quality growth. None of the children in the control group improved in both components of growth quality simultaneously during this period. Three (7 per cent) improved in one and maintained their position in the other; one (2 per cent) did not change in either component; six (15 per cent) improved in one component but lost ground in in the second; ten (24 per cent) fell off in one component while maintaining their positions in the second; and twenty-one (51 per cent) fell off in both components. The quality of growth of the older children, in general, was superior to that of the younger children, a finding which was noted in children in both the test and control groups during this period.

The Postmilk Period.—The changes in the quality of growth which occurred in the children in both the test and control groups in the postmilk period are presented in Table II. In six (15 per cent) the quality of growth

improved in both components, five (12 per cent) improved in one and remained unchanged in the other, in one (2 per cent) there was no change in either speed or direction of development, two (5 per cent) improved in one component but fell off in the other, fifteen (37 per cent) lost position in one component and remained unchanged in the second, while twelve (29 per cent) fell off in both speed and direction of development. In contrast, the corresponding values for the forty control children were three (7.5 per cent), three (7.5 per cent), four (10 per cent), three (7.5 per cent), eleven (27.5 per cent), and sixteen (40 per cent).

Four of the eleven children in the test group who improved in both speed and direction of development continued their improvement in both of these components of growth quality throughout the postmilk phase, while four lost both speed and direction, one maintained the speed and direction achieved during the period of supplementation, one improved in direction but lost speed, and one maintained direction but lost speed.

THE EFFECT OF THE MILK SUPPLEMENTS ON THE INCIDENCE OF EPISODES OF RETARDED GROWTH

The Milk Period.—The incidence of episodes of retarded growth in the children in the test and control groups during the twenty-month supplementation period is shown in Table I. Each instance of retarded growth was represented on the Grid by a drift down-channel, accompanied by an auxodromic lag which exceeded the limits of tolerance. Eleven (27 per cent) of the children in the test group did not show any episodes of growth failure, while fourteen (34 per cent) underwent one instance of retarded growth, eleven (27 per cent) underwent two, four (10 per cent) underwent three, and one (2 per cent) underwent four. While eight (19.5 per cent) of the children in the control group were free from episodes of retarded growth, thirteen (32 per cent) experienced one, eighteen (44 per cent) experienced two, and two (5 per cent) experienced three. Fig. 8 reveals that the incidence of retarded growth in both the test and control groups during the milk period was greatest in June, July, and August. In eight instances the episodes of growth failure in the children in the test group occurred concomitantly with bouts of infectious disease. Infectious disease accompanied episodes of growth failure in three of the children in the control group.

The Postmilk Period.—The incidence of episodes of retarded growth during the twelve-month postmilk period is shown in Table II. Nine (22 per cent) of the children in the test group made unimpeded progress, twenty-four (58.5 per cent) underwent one instance of retardation, seven (17 per cent) underwent two, and one (2 per cent) underwent three. In contrast, sixteen (40 per cent) of the children in the control group made unimpeded progress during this period, seventeen (42.5 per cent) underwent one instance of retardation, five (12.5 per cent) underwent two, and two (5 per cent) underwent three. The highest incidence of retarded growth in both the test and control groups during this phase occurred in June, August, and October (Fig. 8).

Infectious disease accompanied episodes of growth failure in three instances in the test group and in six instances in the control group. The incidence of growth failure was greater in the younger children in both groups than in the older children, a finding which was observed in both the milk and postmilk periods.

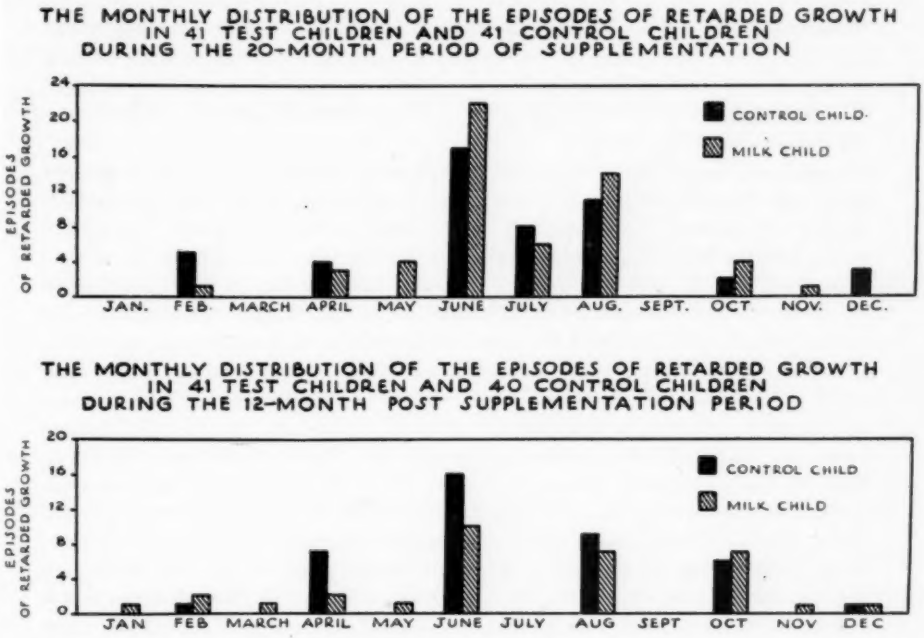


Fig. 8.—The incidence of episodes of retarded growth in the children receiving the milk supplements and in the children in the control group during the milk and postmilk periods. Note the seasonal variations in the incidence of retarded growth in both groups of children.

DISCUSSION

Since by the Grid technique each child is his own basis for comparison, the findings reported in this paper include only those derived from the individual child in each pair rather than from each pair as a single unit.

In analyzing the Grid findings for each child during each phase of the study, it is apparent that the most pronounced difference between the growth patterns of the children in the test and control groups existed in their respective rates of development. The rapid rate of development characteristic of the great majority of the children in the test group during the milk period was dependent to some extent upon the type of milk provided in the supplement. The number of children involved, however, is too small to permit a distinction between the relative effectiveness of the whole and nonfat milk supplements on the basis of the Grid data alone. Only nine of the forty-one children who received the milk supplement progressed at a rate of less than one

isodevelopmental level per month, as contrasted with twenty-five of the forty-one children who did not receive the milk supplement. In the Grid technique the rate of development is measured in terms of the number of isodevelopmental levels gained per month. The isodevelopmental level reached by a child is, in turn, dependent upon his height and weight. It would appear, therefore, that the nutrients supplied by the milk supplements were implicated in some manner with the rapid increases in height and weight observed in the children in the test group. The withdrawal of the supplement resulted in a decline in the rate of development in twenty-two (73 per cent) of the thirty children in whom a rate exceeding one level per month had been noted during the milk phase of the study.

A second significant effect of the milk supplement was the improvement in the speed of development (determined from the changes in the age schedules of development) of many of the children in the test group during the milk phase of the study. Here again this finding is emphasized by the failure of sixteen (73 per cent) of the twenty-two children in this group, whose speed of development increased during the milk period, to continue the improvement when the supplement was withdrawn. In the Wetzel formulation, the speed of development is dependent upon the age of the child and the isodevelopmental levels reached by the child at successive examinations. While it may appear that increases in the *speed* of development should have paralleled those noted for the *rate* of development, it must be recalled that not all of the children in the test group were in the same phase of growth at the same time throughout the study, but that they ranged in growth phase from childhood through adolescence. Since the age schedules of development of the Wetzel Grid are constructed in acknowledgment of the differences in speed during the various phases of growth, it would seem that this factor may account for the lower incidence of increases in speed of development among the children in the test group when compared with the changes in rate of development.

While a significantly larger number of the children in the test group improved in their direction of development as contrasted to the children in the control group, this response was not nearly as widespread as that observed for the rate and speed of development. Because of the width of the Grid channels, the increases in height and weight required to effect a favorable change in the direction of development (as measured by the relation of the child's channel curve to the incline of the channel system) are considerably greater than those required to produce an increase in the rate and speed of development in the same child. Despite the fact that the majority of the children in the test group followed the M to B_4 physique channels on the Grid (Fig. 3), the increases in height and weight in these children during the milk period were insufficient to improve materially the direction of development in twenty-seven of the forty-one cases.

In the Wetzel formulation, the quality of growth is dependent upon the direction of development and the speed of development. The effect of the

milk supplements on each of these components individually has been discussed in detail in the preceding paragraphs. Suffice it to say that whereas the quality of growth improved in eleven of the children in the test group during the supplementation period, this response was not observed in any of the children in the control group. When the supplement was withdrawn only four (37 per cent) of the eleven children continued their improvement. The indications are, therefore, that nutritive failure has a pronounced deterrent effect upon the quality of growth.

An analysis of the number of instances of retarded growth in both groups of children during both phases of the study reveals that for the most part the frequency of episodes of retarded growth followed the seasonal distribution reported in a previous publication.[5] While no significant differences were observed between the two groups of children, as groups, in either phase, it was noted that the instances of retarded growth declined in number as the children approached physical maturity. It would appear that since the children with nutritive failure were, in the main, on progressively slower age schedules of development (Figs. 5 and 6), a point was eventually reached at which the caloric needs required to maintain the slow schedules of development were fulfilled by even a substandard food intake.

SUMMARY AND CONCLUSIONS

Eighty-two children were paired on the basis of history and evidence of nutritive failure, sex, roentgenographic analyses of the hand, wrist, and forearm, phase of growth, general body type, freedom from contagious and infectious disease and allergy to cows milk, and accessibility of the home and cooperation of the parents. One child in each pair was given a supplement of the equivalent of one quart of either reconstituted whole milk (4¼ ounces of milk solids) or nonfat milk (3 ounces of milk solids) each day, six days per week, for a period of twenty months. Twenty-two children (nine boys and thirteen girls) received the nonfat milk, while nineteen children (nine boys and ten girls) received the whole milk. No changes other than the addition of the milk supplement to the daily dietary of one child in each pair were made in the lives of any of the children selected for this study except those changes which were completely voluntary. Each child, with the exception of one child in the control group, was studied for an additional twelve months after the supplement was discontinued.

This report is confined to a summation of some of the changes in the growth progress of both groups of children which occurred during the milk and postmilk phases of the investigation as measured by the Wetzel Grid. The findings include only those derived from the individual child in each pair rather than from each pair as a single unit. They constitute the following:

1. Only sixteen (39 per cent) of the children who did not receive the milk supplement progressed at a rate of more than one isodevelopmental level per month during the milk phase, as contrasted with thirty (73 per cent) of the children who received the milk supplement.

Only eight (27 per cent) of the thirty children in the test group who had progressed at a rate of more than one isodevelopmental level per month during the milk phase continued to do so in the postmilk period.

2. Only three (7 per cent) of the children who did not receive the milk improved their speed of development during the milk phase, as contrasted with twenty-two (54 per cent) of the children who received the milk supplement.

Only six (27 per cent) of the twenty-two children in the test group who improved their speed of development during the milk phase continued to do so during the twelve-month postsupplementation period.

3. Only six (15 per cent) of the children in the control group improved their direction of development during the milk phase, as contrasted with fourteen (34 per cent) of the children who received the milk supplement.

Only five (36 per cent) of the fourteen children in the test group who had improved their direction of development during the milk phase continued to do so in the postmilk phase.

4. None of the children in the control group improved their quality of growth during the milk phase of the study, while eleven (27 per cent) of the children who received the milk supplement improved in this respect during the same period.

Only four (36 per cent) of the eleven children in the test group who had improved their quality of growth during the milk phase continued to do so following the withdrawal of the supplement.

5. No attempt was made in this report to correlate the Grid findings alone with the type of milk supplement because of the small number of children receiving the whole milk supplement (nine boys and ten girls) and the nonfat milk supplement (nine boys and thirteen girls).

6. The Wetzel Grid proved to be a useful method for measuring certain changes in the growth progress of children with chronic nutritive failure when a known amount of milk was added to their daily dietaries. The growth of every child, however, is a phenomenon specific for that child, and such aids as the Wetzel Grid must be interpreted in the general light of the sum total information which can be acquired from the large variety of factors which influence growth progress.

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ANTIHISTAMINIC DRUGS IN PEDIATRIC ALLERGY

LEO H. CRIEP, M.D., AND THEODORE AARON, M.D.
PITTSBURGH, PA.

APPROXIMATELY 10 per cent of the population develop the common major allergies. Of these, one-third begin to have symptoms within the first decade. The practice of allergy, therefore, is an integral part of the practice of pediatrics. Without doubt, the early recognition and institution of adequate therapy in allergic children is imperative, first, because it is therapeutically satisfactory, and second, because diseases of sensitivity, if allowed to carry on unchecked, may lead to irreversible pathologic changes which are difficult to treat successfully.

Most of the allergic states may be seen in children. There are some differences, however, in their diagnosis and management. Nasal allergy in the child often is mistaken for the common cold. Bronchial asthma, which may start as an allergic cough, may be mistaken for a recurrent infective bronchitis. Disfigurement of the face in allergic rhinitis, or disfigurement of the chest in bronchial asthma is always a possible complication of untreated respiratory allergy. Allergic conditions may not only make children irritable but may also affect their growth.

Good therapeutic results, however, usually are obtained in allergic children. As a rule no irreversible pathology has been created and the children respond quickly to correct therapy. However, symptomatic relief frequently is necessary. This not only creates confidence but also if the irritability of the child is decreased, allergic investigation is made much easier. Occasionally it is necessary to give some form of adjunct therapy to a child whose condition does not respond to hyposensitization treatment. It is in these instances that antihistaminic drugs have proved so useful.

ROLE OF HISTAMINE IN ALLERGY

Anaphylaxis and certain allergic manifestations are analogous immunologically in many respects. The manifestations of both are due to an antigen-antibody union which irritates the cells of certain tissues, which are referred to as shock tissues. As a result of such irritation there occurs in animals smooth muscle spasm (bronchioles in the guinea pig and media of arterioles in the rabbit); in man there occurs both smooth muscle spasm and dilatation and increased permeability of capillaries. For a long time investigators have tried to find out just what produces this irritation. This question was finally answered by Lewis, who concluded as a result of his investigations that the antigen-antibody union releases in the tissues either histamine or a histaminelike substance and that it is this chemical which produces reversible tissue changes charac-

From the Department of Medicine, Section on Allergy, School of Medicine, University of Pittsburgh.

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teristic of anaphylaxis or allergy. He pointed out the similarity between histamine shock and anaphylactic shock, as well as the similarity between the positive skin reactions obtained from the intradermal injection of histamine and the injection of the specific allergen in a sensitive individual.

Histamine has the property of causing contraction of the guinea pig uterine strip and produces a fall in the peripheral blood pressure of the cat. Injected intradermally in man, it produces a local change which has been described as the triple response of Lewis. It consists of (1) erythema, (2) flare, and (3) whealing. This triple response is identical with that produced on the skin of a dermographic patient by mechanical irritation such as scratching. The administration of histamine in large doses produces profound vasodilatation with loss of circulating fluid and reduction in cardiac output. Histamine apparently acts directly on capillaries without the intervention of the nervous mechanism, dilating these capillaries and producing increased capillary permeability. This effect does not involve equally all the smaller arterioles and capillaries. For example, while the vessels of the face and neck are dilated, those in the extremities are contracted, accounting for the marked difference in the skin temperature of the extremities and of the face after histamine administration. Salivary, gastric, and bronchial mucous glands are stimulated. The blood pressure is lowered. The smooth muscle of the bronchi, intestines, and uterus is contracted. Clinically, there occurs dizziness, headache, and flushing of the face. Symptoms resembling those of histamine administration may result in patients with allergy to physical agents. These include, as is shown by one of our cold-sensitive patients, local whealing on contact with cold followed by flushing of the face, dizziness, and lowered blood pressure.

In view of this all-important role played by histamine or an H-like substance in the mechanism of allergic manifestations, it is logical that efforts should have been directed for many years toward the discovery of some agent which would combat this histamine-like influence on the tissues. Such an agent would have to possess the property of either (1) destroying histamine chemically, (2) descreasing the susceptibility of the shock tissue to histamine, or (3) in some way interfering between the union of antigen and antibody so that this union will not result in histamine liberation and (4) stimulating the sympathetic nervous system.

The following agents have been tried with disappointing results as antihistaminic agents.

HISTAMINASE

Best and McHenry showed in 1930 that extracts of fresh tissues such as the kidney and the intestines contain an enzyme and that this enzyme can destroy histamine in the test tube. It was natural to assume that the introduction of this enzyme (histaminase) into the body of an allergic patient in large quantities might help counteract the effects of histamine. Extensive clinical use of histaminase in various allergic disorders such as urticara, hay fever, and asthma prove this drug to be of very little value. Administration of the drug does not interfere with the direct skin test or with the passive transfer reaction.

HISTAMINE-AZO-PROTEIN (HAPAMINE)

Hapamine has had wide usage in the treatment of allergic disorders. Histamine is a substance of small molecular weight, rapidly dialyzable and in itself not antigenic. However, it can be rendered antigenic by combining it or conjugating it with some protein (haptene). Working with this combination (histamine-azo-protein), Fell demonstrated that precipitins are formed by injecting rabbits with this substance and that these precipitins are specific for the histamine part of the compound. The administration of histamine-azo-proteins in man stimulates the formation of specific precipitins in the serum. It is also shown that histamine may be neutralized in vitro by the sera of patients treated with histamine-azo-protein. However interesting these laboratory results may be, our experience and that of others indicates that histamine-azo-protein (Hapamine) is not effective in the treatment of allergic disorders.

HISTAMINE

An attempt has been made to increase histamine tolerance by the administration of increasing doses of histamine. This has been carried out either by the subcutaneous administration of a solution of histamine acid phosphate, or by the administration of 2.75 mg. of histamine acid phosphate in 300 c.c. of normal saline intravenously daily for six successive days. It is interesting to point out that the administration of histamine subcutaneously or intravenously does not reproduce clinical allergic manifestations such as asthma or hay fever in an allergic individual, nor is there any agreement of opinion that this form of therapy either helps to increase the tolerance of the patient to histamine or that it results in any clinical benefit. Histamine therapy is said to be effective in the treatment of a certain type of chronic vascular headache (histamine cephalgia), although the mechanism of its effect is not clearly understood.

ANTERGAN AND NEO-ANTERGAN

French investigators were working as early as 1932 on a series of chemicals for which the tissues would have a greater affinity than for histamine. Antergan (*N'*phenyl-*N'*benzyl-N-dimethylethylenediamine) and later Neo-Antergan ($C_{21}H_{27}N_3O_5$) (Ethylenediamine, N-p-methoxybenzyl-*N'*, *N'*-dimethyl-N-2-pyridymaleate) were finally discovered. Both of these are potent antihistaminic drugs in that if they are injected subcutaneously into guinea pigs they will protect the animal against the fatal result obtained from the administration of many times the fatal dose of histamine. Of the two, Neo-Antergan is more potent and less toxic. The drug has been introduced recently on the American market but is still being investigated. The dose is 50 to 100 mg. and the drug is available in coated tablets.

AMERICAN ANTIHISTAMINIC DRUGS

These drugs were followed later by Benadryl and Pyribenzamine, which were produced in this country. The latter agents have received attention for their clinical value in certain allergic states. However useful these drugs may

be, they have certain disadvantages. They often cannot be used in adequate doses in pediatric practice because of their unpleasant and frequent side reactions which include drowsiness, headache, and dizziness.

NEOHETRAMINE

Neohetramine, a recent histamine antagonist, has been shown by us to have potent antihistaminic, antianaphylactic, and antiwhealing properties. Studies with both animals and adult humans illustrate its low toxicity.

The therapeutic results in the symptomatic treatment of allergic diseases in the adult by the use of Neohetramine compare favorably with the results obtained from other similar drugs. Reference to Table I indicates that the best results were obtained in hay fever, allergic rhinitis, and urticaria.

TABLE I. CLINICAL EFFECTS OF NEOHETRAMINE ON ADULTS

NO.	DIAGNOSIS	NONE (%)	SLIGHT (%)	MODERATE (%)	COMPLETE RELIEF (%)
124	Hay fever	18	22	27	33
41	Allergic rhinitis	20	27	24	27
33	Bronchial asthma	37	24	27	12
11	Atopic dermatitis	18	73	9	0
20	Urticaria	25	25	20	30
6	Migraine	17	33	0	50
8	Contact dermatitis	0	38	50	12

CHEMICAL EFFECTS OF NEOHETRAMINE ON CHILDREN

The present clinical study on children was carried on with Neohetramine (2-(N-methoxybenzyl-N-dimethylamino-ethyl)-aminopyrimidine monohydrochloride). Neohetramine is available in the following forms: elixir Neohetramine 25 mg. to the dram, and in the form of tablets of 50 mg. and 100 mg. doses. A total of 232 infants and children received Neohetramine for the symptomatic relief of various allergic disorders, for a period ranging from two weeks to four months. The patients varied in age from 6 months to 12 years. The dose was one dram of the elixir every four hours for infants up to 4 years of age and 50 mg. every four hours for older children. The drug was administered only when symptoms were present. When relief was obtained from a given dose, it lasted, as in the case of other antihistaminic drugs, for a period of three to six hours. When effective, one dose taken at bedtime would quiet the child and enable him to sleep for the night. The results as seen in Table II were divided into no relief, moderate, and complete relief from symptoms.

Placebo controls were used in a control group of ten patients with allergic rhinitis, twelve cases of seasonal hay fever, thirteen cases of urticaria, twenty cases of bronchial asthma, and five cases of atopic dermatitis. In many instances the drug was discontinued and then readministered a few days later in order to observe its repeated effect.

Children suffering with hay fever received the drug throughout the duration of the season. In patients with allergic rhinitis, bronchial asthma, and urticaria, its administration was continued over periods of two to four

TABLE II. NEOHETRAMINE IN ALLERGIC CHILDREN

	TOTAL NO. PATIENTS	NO RELIEF		MOD. RELIEF		MARKED RELIEF		SIDE ACTIONS
		NO.	%	NO.	%	NO.	%	
Allergic rhinitis	61	11	17	22	35	28	48	6
Hay fever	47	5	10	17	36	25	54	4
Urticaria and Angioneurotic edema	22	3	14	7	31	12	55	3
Bronchial asthma	66	46	70	14	21	6	9	4
Atopic dermatitis	21	10	50	8	40	3	10	1
Contact dermatitis	9	7	78	1	11	1	11	0
Physical allergy	3	—	—	—	—	3	100	0
Gastrointestinal allergy	3	1	33	2	66	0	—	0

months. This was done in order to study the therapeutic effect of the drug, but also in order to discover possible toxic influences of its prolonged administration. Repeated urine, blood count, blood chemistry, and electrocardiographic examinations failed to reveal any evidence of such toxic effects.

Allergic Rhinitis.—A total of sixty-one children with allergic rhinitis received the drug for periods ranging from two weeks to two and one-half months. Of this number, 17 per cent received no relief, 35 per cent had moderate relief, and 48 per cent had complete relief of symptoms while the drug was given. The nasal obstruction and rhinorrhea as well as the itching were relieved when the drug was therapeutically effective.

Hay Fever.—A total of forty-seven children suffering with seasonal hay fever received Neohetramine in amounts referred to above for various intervals during the duration of the hay fever season. Fourteen of these children either had no preseasonal pollen therapy or the amount of treatment received by them was considered inadequate. Only 10 per cent of the total number of patients receiving Neohetramine did not respond. Thirty-six per cent had moderate relief and 54 per cent were so completely relieved that the patients asked for a refill of their prescription when the available supply of the drug was exhausted. This relief was obtained equally in the treated and untreated hay fever group, that is, in patients whose symptoms were mild and who received proper prophylactic pollen therapy, as well as in the untreated group in which the symptoms were severe. No differences in the effectiveness of the drug were observed in those sensitive to grasses, fungi, or ragweed.

Urticaria and Angioneurotic Edema.—The results in a total of twenty-two children with urticaria were as follows: (1) 14 per cent were not relieved; (2) 31 per cent were moderately relieved; and (3) 55 per cent were completely relieved of symptoms. The drug does not prevent the recurrence of urticaria but brings about quick relief once the lesions appear.

Bronchial Asthma.—Sixty-six patients with bronchial asthma were studied. These were for the most part due to allergy to exogenous substances and not accompanied by any complications. The drug was given in adequate doses over a period of several weeks at a time and then repeated at a later date. The results were equally disappointing in asthma of various degrees of severity. Seventy per cent of all patients were not relieved at all, 21 per cent were moderately relieved, and 9 per cent were markedly relieved.

Atopic Dermatitis.—The clinical results in a total of twenty-one patients with atopic dermatitis were studied. Fifty per cent of this group were not relieved at all. Forty per cent seemed to have less itching and 10 per cent claimed complete relief. It is difficult to interpret these results because other treatment was used concomitantly and because it was difficult to evaluate psychogenic factors. Neohetramine ointment (2 per cent) was also used locally in these cases with results which are not too encouraging. Many of the twelve children in whom local application of the drug was employed stated that they obtained some relief at first, but later the annoying pruritis reappeared and in none of the cases was the dermatitis improved as compared with other involved areas which remained untreated. This experience is similar to that obtained with the local application of other antihistaminic drugs.

Contact Dermatitis.—Neohetramine did not offer much relief in contact dermatitis, regardless of whether the drug was administered orally or applied locally. A total of nine children were studied. Four of these had poisin ivy dermatitis. Seventy-eight per cent were not at all benefited. Eleven per cent were moderately and eleven per cent were markedly improved. This series is small but sufficient to warrant the above conclusions.

Physical Allergy.—Of three children studied, two were sensitive to cold and one was allergic to sunlight. All of these patients were improved symptomatically.

Gastrointestinal Allergy.—Three children suffering with gastrointestinal symptoms due to food allergy were improved symptomatically by Neohetramine. One child sensitive to milk could take moderate quantities of milk after the drug was taken previously.

Side Reactions.—Of the 232 patients who used Neohetramine, only 18 or 8 per cent had any side reactions. This is somewhat less than observed in adults. These reactions consisted of restlessness, insomnia, constipation, rhinorrhea, drowsiness, and headache in the order of frequency. In only four of these children was it necessary to discontinue the drug because of these reactions. This percentage of side reactions is certainly a great deal lower than that found from the use of benadryl and pyribenzamine as well as many other antihistaminic drugs.

CONCLUSIONS AND SUMMARY

Neohetramine is a potent new antihistaminic drug. The therapeutic results obtained from the use of this drug in the symptomatic treatment of allergic disorders in infants and children of all ages compares favorably with the results obtained from other antihistaminic agents.

It is interesting to point out that some children will be relieved by one antihistaminic drug and others by a different drug. The side reactions obtained from Neohetramine are definitely lower than those observed from the use of other drugs and therefore its use is safer in children. No serious side reactions or fatalities have been reported. Careful observation of children receiving the

drug over periods as long as three months fail to reveal any effect on blood pressure, pulse rate, urine, or blood count.

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LEUCEMIA IN CHILDHOOD

A Clinical and Roentgenographic Study of Seventy-Two Cases

John H. Dale, Jr., M.D.
New York, N. Y.

LEUCEMIA in childhood is a fatal systemic disease affecting chiefly the blood forming organs of the body. At some time during the course of the disease, abnormal leucocytes can be demonstrated in the peripheral blood, the bone marrow, or both. The cause of the disease is not known but it is generally accepted that leucemia is related to the neoplastic group of conditions.

The purpose of this paper is to present a review of the clinical and roentgenographic findings in a large series of cases of leucemia occurring in infants and children.

MATERIAL

The patients comprising this study were observed on the pavilions of the Children's Clinic at the New York Hospital from September, 1932, to June, 1948. During this period the diagnosis of leucemia was made for seventy-two infants and children on the basis of clinical, hematologic or autopsy findings either singly or in combination.

RESULTS

Incidence.—Leucemia is relatively uncommon in infants and children. During the period covered in the study, the incidence was 0.42 per cent of all admissions to this general pediatric service. Despite this low incidence, leucemia, occurring in seventy-two juvenile patients, was the most frequently encountered malignant condition. It surpassed in number the combined malignant tumors of the brain (17), kidney (9), adrenal (6), eye (4), and bone (2), as well as the related lymphoblastomas; Hodgkin's disease (9), and lymphosarcoma (2).

Sex and Age Distribution.—The sex and age distribution of the seventy-two patients is presented in Table I. Thirty-eight, or 52.7 per cent, of the patients were boys. The usually reported predominance of males in the early years of life was not noted. Actually, during the first four years girls showed a slightly higher incidence of the disease. In the second five years the number in girls fell and, conversely, the incidence in boys showed an increase after the first semidecade. The figures for the age group between ten and fifteen years are incomplete since children over the age of 13 years are not admitted to the pediatric service. Despite the incompleteness in the third semidecade, there appeared to be a continuing decrease in the incidence among girls and an increase among boys.

From the New York Hospital and the Departments of Pediatrics and Radiology, Cornell University Medical College.

TABLE I. SEX AND AGE (SEVENTY-TWO CASES)

AGE (YR.)	MALE	FEMALE	NO. CASES	PER CENT	
				MALE	FEMALE
0-1	1	1	2	50.0	50.0
1-2	1	4	5	20.0	80.0
2-3	6	7	13	46.2	53.8
3-4	4	6	10	40.0	60.0
4-5	6	1	7	85.7	14.3
	18	19	37	48.65	51.35
5-6	5	2	7	71.4	28.6
6-7	5	4	9	55.6	44.4
7-8	2	3	5	40.0	60.0
8-9	0	0	0	—	—
9-10	2	3	5	40.0	60.0
	14	12	26	53.9	46.1
10-11	2	2	4	50.0	50.0
11-12	1	0	1	100.0	—
12-13	3	1	4	75.0	25.0
	6	3	9	66.67	33.33
Total	38	34	72	52.70	47.30

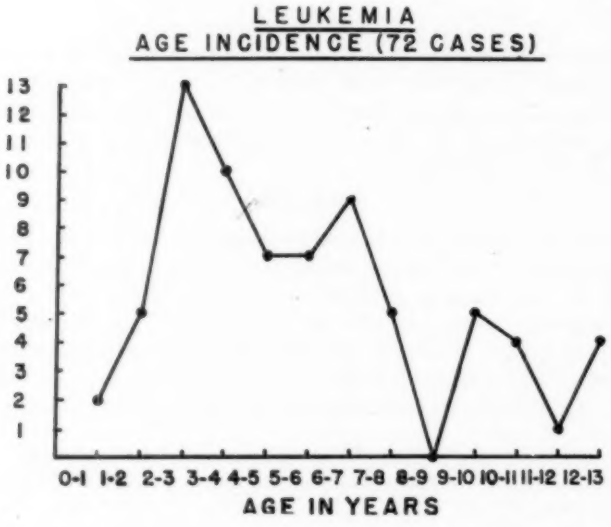

Fig. 1.

The age incidence is plotted in Fig. 1. It ranged from 10 months to 12¾ years. The peak was in the third year of life and the majority of cases occurred in the first five years. Except for a secondary rise of questionable significance in the seventh year, the incidence tended to decrease steadily after the third year.

The figures for sex and age distribution in this series are similar to those reported by Cooke[1] in 1942 in his review of 1,500 cases of childhood leucemia.

TABLE II. DURATION OF LEUKEMIA (THIRTY-NINE PATIENTS)

TIME (MO.)	NO.	%
0-1	2	
1-2	6	
2-3	6	
3-4	2	
4-5	8	
5-6	3	
Subtotal	27	69.2
6-7	3	
7-8	1	
8-9	1	
9-10	2	
10-11	0	
11-12	1	
Subtotal	8	20.5
Total	35	89.7
Over 12	4	10.3

Duration.—The course of leucemia in childhood is characteristically acute, rapidly progressive, and fatal within a few weeks or months from the onset. The duration of the disease, as estimated from the time of appearance of the first symptom to the time of death of the patient, is shown for thirty-nine patients in Table II. Thirty-five patients, or 89.7 per cent, died within one year; twenty-seven, or 69.2 per cent, within six months of the onset of symptoms. The range was two weeks to two ten/twelve years. Three patients survived one and one-half years or longer. Hematologic and necropsy findings revealed that the latter had a chronic form of leucemia.

Clinical and Hematologic Classification.—The acute form of leucemia is most frequent during childhood, as shown in Table III. Chronic forms do occur but they are rare. In this series, sixty-nine, or 95.8 per cent, of the patients were classified as having acute leucemia on the basis of the clinical course and hematologic studies; three, or 4.2 per cent, were diagnosed as chronic.

TABLE III. CLASSIFICATION—CLINICAL AND HEMATOLOGIC (SEVENTY-TWO CASES)

CLASSIFICATION			NO.	%
Acute			69	95.8
Lymphoid		46		
Myeloid		22		
myeloblastic	(16)			
myelocytic	(6)			
Monocytoid		1		
Chronic			3	4.2
Lymphoid		1		
Myeloid		2		
Total			72	100.0

Hematologic classification was made in the conventional manner on the type of abnormal leucocyte appearing in the peripheral blood, the sternal marrow, or both. The high frequency of diagnosis of the acute myeloid type of leucemia is thought to be related to the introduction in 1937 of sternal marrow aspiration and to the increased ability of members of the staff to recognize abnormal leucocytes.

Symptoms and Physical Findings.—It is recognized generally that childhood leucemia has no characteristic symptom complex and that it is often extremely protean in its early manifestations, closely simulating many of the acute and subacute diseases of this period.

Fourteen, or 19.2 per cent, of the seventy-two patients gave a history of infection prior to the onset of the disease. With one exception the infection was acute tonsillitis or pharyngitis. In this exception, symptoms of leucemia followed scarlet fever. This low incidence of preceding infection lends little support to the infectious theory of the cause of leucemia.

A number of symptoms such as fever, malaise, fatigue, loss of appetite, and irritability are nonspecific and are common to many childhood diseases. There is, however, a group of relatively constant symptoms resulting from involvement of the various organ systems by leucemic cells which is of aid to the clinician in diagnosis. Chief among these symptoms are pallor, hemorrhagic manifestations, bone and joint pain, and enlargement of the lymph nodes. Table IV presents the most frequently encountered symptoms in the seventy-two patients studied.

TABLE IV. SYMPTOMATOLOGY (SEVENTY-TWO CASES)

SYMPTOM	NO.	SYMPTOM	NO.
Fever	44	Joint pain	11
Pallor	40	Enlarged cervical nodes	11
Hemorrhagic tendencies	38	Joint swelling	11
Loss of appetite	24	Weight loss	10
Fatigue	22	Facial edema	5
Bone pain	17	Vomiting	3
Preceding infection	14	Irritability	3
Abdominal pain	12	Enlarged axillary nodes	2

The physical findings in our patients differed in no essential respects from those described in standard pediatric textbooks.[2, 3] It is of interest that the presence of fever, bone and joint swelling and tenderness, and a systolic heart murmur in the absence of lymphadenopathy, hepato- and splenomegaly in some patients suggested the diagnosis of acute rheumatic fever. The chief physical signs observed in this series are listed in Table V.

TABLE V. PHYSICAL FINDINGS (SEVENTY-TWO CASES)

FINDING			NO.
Fever			72
Pallor			72
Heart murmur			65
Hepatomegaly			64
Hepato + splenomegaly			54
Hemorrhagic manifestations			52
petechiae	37	in combination	
ecchymoses	27		
bleeding gums	19		
retinal hemorrhage	6		
Generalized adenopathy			36
Bone tenderness			6
Joint swelling			2

Laboratory Findings.—Sixty-nine, or 95.8 per cent, of the patients had varying degrees of anemia at the time of admission; the remainder developed anemia during the course of the disease. Hemoglobin values (Sahli) ranged from 3.0 to 10.5 Gm. per 100 c.c.; the red cell counts, from 500,000 to 3,500,000 per cubic millimeter.

Initial leucocyte counts ranged from 640 to 600,000 per cubic millimeter with twenty-three patients having a total white cell count of less than $10,000^3$ per cubic millimeter on admission, and an additional fifteen showing a fall below 10,000 per cubic millimeter at some time during the course of the disease. Only two patients with an initial leucopenia showed a subsequent increase above $10,000^3$ per cubic millimeter.

Peripheral platelet counts were recorded in fifty-nine patients. In fifty-three of these the counts were below $100,000^3$ per cubic millimeter or the platelets on blood smears were reduced or absent. In forty-eight of these latter patients, signs of hemorrhage were present, the common sites being the skin, retinae, or gums. Only six patients had normal platelet counts and four of these showed bleeding tendencies. Actual leucemic involvement of the blood vessels was presumed to be responsible for the bleeding in these cases.

Bleeding times were prolonged, clotting times normal, and clot retraction delayed or absent in all recorded instances.

Abnormal leucocytes were present in the peripheral blood at some time during the course of the disease in all cases. Identification of the type of abnormal cell was often difficult, requiring subsequent sternal marrow studies and oxidase stain to validate initial identification.

Sternal marrow aspiration biopsies were employed in fifty-four patients and in all cases abnormal leucocytes were demonstrated in the marrow tissue. The marrow was hyperplastic in the majority of cases with a depression of erythropoietic tissue paralleling the peripheral anemia. Megakaryocytes were recorded as lowered or absent in all cases showing a reduction of peripheral platelets.

Roentgenographic Changes in the Long Bones.—The literature contains many reports of the roentgenographic changes in the long bones in childhood leucemia. Most of the reports, however, present isolated cases or small series of cases and they may have created the impression that osseous changes in the long bones in this condition are uncommon.

In the few reports of large series of cases, the incidence of osseous change has been over 50 per cent. Baty and Vogt[4] in 1935 demonstrated roentgenographic changes in the long bones in over 70 per cent of forty-three patients. Kalayjian, Herbut, and Erf[5] surveyed the literature up to 1946 and found 144 children with leucemia in whom bone changes were reported and they added two of their own cases. More recently, Landolt[6] demonstrated osseous changes in 75 per cent of a series of forty-eight children. In his comprehensive review of 103 children with leucemia, Silverman[7] found the incidence of skeletal changes to be over 50 per cent. In the present series osseous lesions were noted in 72.5 per cent of the forty infants and children in whom roentgen examinations of the long bones were available.

TABLE VI. ROENTGENOGRAPHIC CHANGES IN THE LONG BONES (FORTY CASES)

	NO.	PER CENT
Cases with roentgenographic changes	29	72.5
a. Transverse radiolucent band	27	93.1
b. Osteolysis	12	4.1
c. Periosteal elevation	7	2.4
Cases without roentgenographic changes	11	27.5

The various lesions found in the skeletal system in childhood leucemia have been described in the literature. Four main types have been reported: (1) a transverse band of diminished density in the metaphyses of the long bones immediately adjacent to the epiphyseal plate; (2) Osteolysis. (3) Periosteal elevation and new bone formation; (4) Osteosclerosis.

The lesions tend to occur in combination in individual patients but solitary bone changes may appear. The incidence and types of osseous change found in our forty patients are shown in Table VI.

Fig. 2.—Transverse bands of diminished density in the metaphyses of the distal femori and proximal tibiae in a male patient aged 8 years with acute lymphoid leucemia.

The most frequently encountered lesion was the transverse band of diminished density in the metaphyses of the long bones. This change was described first by Baty and Vogt[4] in 1935. In our experience the band was the first skeletal change in the majority of patients and it was the sole osseous change in thirteen of the twenty-nine patients manifesting skeletal lesions. It tended to appear in the areas of most rapid growth: the distal femora, tibiae, radii, and ulnae in decreasing order of frequency. It was not noted in areas

of slow growth such as the proximal ulnae and radii. The distribution in individual patients tended to be widespread and symmetrical. The band varied from 1 to 7 mm. in width and tended to become more clearly defined as the disease progressed. Recognition of the band in one patient thirty days following a completely negative roentgen study of the long bones demonstrates that it can appear within a relatively short period of time. One patient with a transient remission of her clinical and hematologic findings revealed a complete disappearance of the band during a period of one and one-half months. This observation suggests that this osseous change is reversible. In the early stages of the disease in several patients, the band was incomplete and extended only partially across the metaphysis. As the disease progressed, serial roentgenograms revealed complete extension across the entire width of the metaphysis. In a few cases it was difficult to distinguish between the band and osteolysis in the metaphyses. The exact nature of the process responsible for the appearance of this lesion is not clearly understood. In one patient the region of the band at autopsy was found to be occupied by hemorrhage. Erb[8] in 1934 found the area to be occupied by leucemic cells and considered that local pressure necrosis of the spongiosa by the proliferating leucemic cells produced the lesion shown on roentgen examination. The widespread distribution of the band in our patients and the presence of an identical band in scurvy, congenital syphilis, congenital biliary atresia, cystic fibrosis of the pancreas, in a few apparently healthy newborn infants, and in patients suffering from chronic disease associated with malnutrition suggests that nonspecific interference with endochondral bone formation may play a role in its production.

Osteolysis was the next most frequently encountered lesion in the series. According to Erb,[8] the lesion is due to atrophy and pressure necrosis of the spongiosa and the compacta of the bone by proliferating leucemic cells. Autopsy findings in several of our cases revealed the presence of leucemic cells in areas of destruction corresponding to the areas of osteolysis seen on roentgen examination. This lesion was found in twelve patients. It never appeared as an isolated lesion but always was associated with the transverse band of diminished density or with periosteal elevation. The osteolysis was widespread and tended to be symmetrical, involving the distal rather than the proximal portions of the bones. In no case was the lesion confined to a single bone. In several patients the small tubular bones of the hands and feet were involved, and in a few patients destructive changes were noted in the iliac bones, mandible, ribs, skull, and vertebrae. The lesions varied from small, irregular areas of radiolucency localized to the shafts or metaphyses to diffuse destruction of the cortex and trabeculae, which in one case gave rise to pathologic fractures of the involved bones.

Periosteal elevation with new bone formation was the third most frequent roentgenographic change. The appearance of the lesion differed in no

Fig. 3.—Diffuse osteolysis of the femur. There are no sclerotic or productive changes except for the new subperiosteal bone formation. Female patient, aged 6 years, with acute lymphoid leucemia.

Fig. 4.—Periosteal elevation involving the humerus, ulna, and radius. The bones also show a diffuse osteolysis. No productive changes are present. Female patient, aged 6½ years, with acute lymphoid leucemia.

respect from that recorded by Taylor,[9] Karelitz,[10] and Kalayjian, Herbut, and Erf.[5] The elevation tended to involve one or more of the long bones. It was noted as a linear density parallel to but separate from the shaft of the bone and either involved segments of the shaft or cloaked the bone. In all seven patients in which it appeared, the elevation was associated with osteolytic lesions. In two patients the small tubular bones of the hands and the feet were involved. The new bone tended to be deposited in a smooth, regular fashion except in two patients, in whom the deposition was rough and

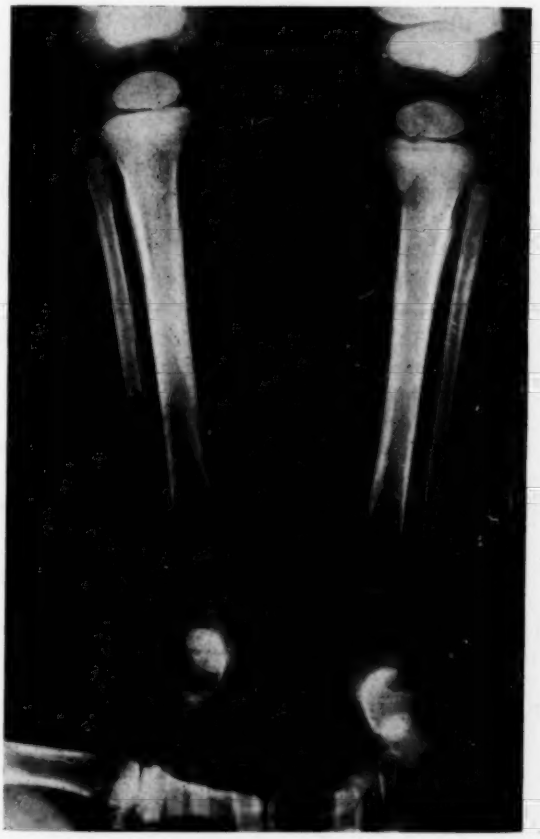

Fig. 5.—Periosteal elevation and new bone formation. Male patient, aged 4½ years, with acute lymphoid leucemia.

irregular. Proliferating leucemic cells which had lifted the periosteum from the shaft were found in the subperiosteal area by Kalayjian, Herbut, and Erf.[5] Microscopically new subperiosteal bone formed from osteoblasts may be deposited parallel to or at right angles to the longitudinal axis of the shaft.

The fourth osseous change, osteosclerosis, was not noted in this series. It is usually a late change resulting from stimulation of osteoblasts and the

formation of new bone or the fibrous and osseous repair of destroyed areas within the bone. Perhaps the absence of osteosclerosis in this series is attributable to failure to obtain serial roentgenograms of the long bones of the patients as the disease progressed. In four recent cases not included in this series, sclerotic changes were noted in the long bones on serial examinations over periods of several months during the course of the disease.

No correlation between the sex of the patients and the frequency of appearance of osseous change was noted in this study. However, there was a definite relationship between the age of the patients and the incidence of skeletal lesions. Although only thirty-seven, or 51 per cent, of the seventy-two patients in the series were less than 6 years of age, twenty-one, or 72.4 per cent, of the twenty-nine patients with bone changes were under 6 years of age. Similarly, although only twenty, or 28 per cent, of the seventy-two patients in the series were less than 4 years of age, fifteen, or 51.7 per cent, of the twenty-nine patients with bone changes were under the age of 4 years.

Eighteen, or 62.5 per cent, of the patients with skeletal lesions had the acute lymphoid type of leucemia.

The incidence of osseous changes in the series increased as the duration of the disease increased. The average duration in patients with bone lesions was eight weeks while those with no demonstrable lesions averaged two weeks. Serial roentgenograms of the long bones of several patients revealed the appearance of bone changes as the disease progressed. Again it is probable that the over-all incidence of osseous lesions in this series would have been higher if serial studies had been obtained in all patients.

All twenty-nine patients with osseous changes on roentgen examination showed involvement of the knee area. The constancy of this may present the radiologist and the clinician with a simple screening measure in suspected cases of leucemia in children and obviate the necessity of more expensive and time-consuming skeletal surveys.

DISCUSSION

Osseous changes in childhood leucemia, although frequent, are not specific. The lesions can be produced by any primary, metastatic, or infectious condition which leads to proliferation of normal or abnormal cells in the bone marrow. Sympathicoblastomas of the adrenal gland, metastasizing to the skeletal system, may produce a picture identical to that of leucemia. Scurvy, congenital syphilis, osteomyelitis, and rickets may also produce many of the changes encountered in leucemia. Conditions which interfere with the normal sequence of endochondral bone formation may produce the transverse band of diminished density. The presence of the described osseous lesions in a child, especially if associated with unexplained fever, hemorrhagic tendencies, pallor, bone and joint pain, should nevertheless alert the clinician to the possibility of leucemia and lead to a complete hematologic investigation.

Leucemia in childhood often is mistaken for rheumatic fever in its early stages. Smith[11] called attention in 1933 to a patient with leucemia in whom the complaint of bone and joint pain and the finding of joint swelling suggested the diagnosis of acute rheumatic fever. Peripheral blood studies did not sug-

gest leucemia. Failure to respond to salicylates and a favorable response to transfusion led to doubt of the initial diagnosis. Roentgen studies of the long bones revealed the changes commonly associated with leucemia. Further investigation, including lymph node biopsy, established the diagnosis. In this series, the complaint of bone and joint pain, the presence of fever, and a systolic heart murmur in the absence of hepato- and splenomegaly led to the initial diagnosis of rheumatic fever in two patients. Roentgen examination of the long bones in both patients revealed changes consistent with leucemia. Further studies, including sternal marrow aspiration biopsy, proved the diagnosis of leucemia.

Cooke[12] called attention to the frequency of bone pain in childhood leucemia. This symptom is thought to be due to increased intraosseous tension secondary to the proliferation of the leucemic cells. Seventeen patients in this series manifested varying degrees of bone pain, and the fourteen who had available roentgenograms of the long bones all showed osseous changes. In addition, sternal marrow studies revealed the presence of abnormal leucocytes in each of these fourteen patients.

Although roentgen examination of the skeletal system is of value in suggesting the diagnosis of leucemia in childhood, it is not as reliable or as sensitive as sternal marrow aspiration. According to Erb,[8] leucemic cells were seen proliferating throughout the bone marrow in the early stages of the disease and yet the roentgenograms revealed no evidence of osseous change. In several of our cases similar findings were noted. Sternal marrow aspiration was employed in fifty-four cases of this series. In all, abnormal cells were demonstrated. In this group osseous changes were found in only 72.5 per cent of forty patients who had roentgenograms.

We believe that both roentgen examination of the long bones and sternal marrow biopsy should be employed to demonstrate abnormal cellular activity in the bone marrow in all suspected cases of leucemia. Examination of the knee area affords a simple, painless, and inexpensive screening method for detection of osseous changes and is a desirable procedure in office practice, outpatient departments, and in situations where sternal marrow aspirations are impractical. Complete skeletal surveys may be obtained in doubtful cases and serial studies of the knee area may prove of value in the detection of lesions suggestive of leucemia. The roentgen examination is also of value in differentiating leucemia from other conditions such as osteomyelitis, rheumatic fever, and rheumatoid arthritis, conditions which may simulate leucemia in its early stages. The presence of bone lesions of the types described in children with fever, pallor, bone pain, and hemorrhagic tendencies demands a thorough hematologic investigation.

SUMMARY AND CONCLUSIONS

1. An analysis of the clinical and roentgenographic findings in seventy-two children with leucemia has been presented.

2. Roentgen examination of the skeletal system is a valuable aid in diagnosis. It is not as specific or reliable as sternal marrow aspiration but aids

materially in the detection of osseous changes suggestive of abnormal marrow activity and points to the necessity for a thorough hematologic study of the patient.

3. Roentgen examination of the knee area provides a helpful screening technique in the investigation of all suspected cases of leucemia.

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INTRAVENOUS PROCAINE IN CHILDREN

DAVID SCHRUM, M.D.
HOUSTON, TEXAS

MANY reports have appeared recently on the use of intravenous procaine, but none of these has discussed its use in children.

Intravenous procaine was given to five children with serum sickness or a related allergic disorder and to one child with a severe burn of 60 to 70 per cent of the body surface. Symptomatic relief in patients with otherwise uncontrolled reactions has been gratifying.

CASE REPORTS

CASE 1.*—N. B., a 5-year-old white boy, received 40,000 units of diphtheria antitoxin on Feb. 4, 1947. Twelve days later, on February 16, he began to complain of generalized itching and his temperature was 101° F. rectally. He had urticaria of his arms, legs, neck, face, and back. He was started on 25 mg. of Pyribenzamine three times a day. On the following day his urticaria had disappeared and he felt fine until late afternoon when he complained several times of slight difficulty in swallowing. On February 20, four days after his initial urticaria, he developed anorexia; his temperature was 100.6° F. rectally and he complained of pain and tightness of his throat. By 7 P.M. he again had generalized urticaria. He was unable to move his legs and had severe muscle and joint pains. Pyribenzamine was stopped at this time.

On Feb. 21, 1947, he was admitted to the hospital where examination revealed an acutely ill boy with a temperature of 101.8° F. rectally and a pulse rate of 138 per minute. He had severe generalized urticaria. He had extreme myalgia and arthralgia and cried from pain elicited by light palpation of the muscles of his lower extremities. There was slight edema of the knee and ankle joints. Flexion of the knees was limited by pain to about 25 degrees. There was some abdominal distention, and he had generalized small, firm, nontender, lymph nodes.

Complete blood count was normal except for a total leucocyte count of 12,800 with a normal differential. There was no eosinophilia. Urinalysis was negative. Conjunctival and intradermal tests with 0.1 per cent procaine hydrochloride solution were negative. The urticarial wheals faded for an area of 6 cm. in diameter around the site of the intradermal injection.

About twenty minutes after the completion of the physical examination he was given 0.25 Gm. of procaine hydrochloride diluted with 250 c.c. of isotonic solution of sodium chloride. This solution was given intravenously by the gravity drip method at a rate of approximately twenty drops per minute. At the end of one hour when about one-half of the solution had run in, the patient felt fine, the urticaria had decreased approximately 75 per cent, and he was able to move his legs freely. He still had slight pain in his knee joints on flexion. By the end of the second hour the administration of intravenous procaine was complete and he was asymptomatic except for a very faint annular urticaria of his elbows and knees. His temperature was normal

From the Department of Pediatrics, The Bowman Gray School of Medicine, Winston-Salem, N. C.

*Patient of Dr. David Greer, treated at St. Joseph's Infirmary, Houston, Texas.

and his pulse rate was 120 per minute. The following day he received three injections of adrenaline in oil and 50 mg. of Pyribenzamine every six hours for three doses because of some recurrence of urticaria. There was no recurrence of muscle or joint pain or edema.

He made a rapid recovery and remained well during the following nine months of observation.

CASE 2.*—M. L., a 5-year-old girl, was admitted to the hospital on March 3, 1947, with a temperature of 100.4° F. rectally, slight swelling, redness, and heat of all large joints, and generalized circinate urticaria.

Complete blood count was normal and urine was negative except for a trace of albumin.

She was given 0.2 Gm. of procaine hydrochloride in 125 c.c. of isotonic saline solution over a two-hour period. All joint manifestations and urticaria had disappeared before completion of the infusion.

She was discharged the following day completely recovered except for a few small areas of urticaria on her extremities.

No cause for this patient's allergic reaction could be elicited by history.

CASE 3.†—C. S., a 4½-year-old boy, was admitted to the hospital on July 11, 1947, with a six-day history of pain in right hip and knee, and transient urticaria. Pain on the day of admission was severe and he had not been relieved by adequate doses of "antihistaminics."

Physical examination was not remarkable except for generalized urticaria and severe pain in his right hip and knee on movement. Complete blood count was normal and the urine was negative.

He was given 0.5 Gm. of procaine in 250 c.c. of physiologic saline solution over a period of fifty minutes and received immediate and permanent relief from pain. During the administration he became restless, irritable, and finally very jumpy. He was given 64 mg. of Sodium Amytal intravenously and symptoms of central nervous system stimulation ceased.

No definite explanation of his illness could be elicited by history.

CASE 4.—J. S., an 11-year-old white boy, was given an injection of tetanus antitoxin (unknown amount) by his local physician on July 4, 1947. He had had one other injection of tetanus antitoxin about three years prior to the present one. There was a familial history of allergy.

On July 10, six days after receiving the tetanus antitoxin, he developed "hives." On July 11 he had aching and swelling of his fingers and knees. Physical examination revealed an acutely ill boy with generalized urticaria and painful and swollen interphalangeal and knee joints. He was given ephedrine sulfate, then adrenaline chloride intramuscularly and finally calcium gluconate intravenously. He received moderate relief for only one hour.

He was sent to the hospital on July 11, 1947, where physical examination revealed an acutely ill boy in severe pain. His temperature was 99.2° F. rectally and pulse rate was 90 per minute. He had generalized urticaria, swollen lips, tongue, and eyelids, and edema of his interphalangeal and knee joints.

Complete blood count was normal except for a white blood cell count of 14,100 with 87 per cent neutrophiles. Urine was negative except for a faint trace of albumin and four plus acetone.

He was given three minims of adrenaline chloride, five minims of adrenaline in oil, and 50 mg. of Benadryl with only slight relief from symptoms. He then developed severe pain in his left hip and edema of his left ankle.

*Patient of Dr. David Greer, treated at St. Joseph's Infirmary, Houston, Texas.

†Patients of Dr. Byron York, treated by Dr. George Salmon at St. Joseph's Infirmary, Houston, Texas (Cases 3 & 4).

At 1:30 P.M., the intradermal test with 0.1 per cent procaine solution was read as negative. Five hundred cubic centimeters of isotonic solution of sodium chloride containing one gram of procaine was started by slow intravenous drip. Only 150 c.c. of the solution had run in at the end of thirty minutes, but the patient had complete relief of all itching and joint pain and partial relief of the edema of his hands and left ankle. The rate of administration was increased and the remainder of the solution was given in only thirty minutes without reaction. The patient had complete relief from itching and pain for five or six hours.

By the next morning, however, the patient had severe pain in his right hip and he was again given intravenously 500 c.c. of isotonic solution of saline containing one gram of procaine hydrochloride over a period of one and one-half hours. He received complete relief from his hip pain but developed slight pain in his right ankle. The following day he was suffering from excruciating pain in both hips and the administration of intravenous procaine was repeated with partital relief from pain. This time the solution was administered at a fairly rapid rate over a period of only one hour and the patient complained of headache, dizziness, and nausea.

After the last administration of intravenous procaine on July 13, 1947, the symptoms of serum sickness gradually subsided and he was discharged from the hospital July 15, 1947, completely recovered. He has had no recurrence.

CASE 5.—W. B., a 4½-year-old boy, entered the North Carolina Baptist Hospital on May 18, 1948. Four weeks prior to entry he was given sulfadiazine by his local physician for acute tonsillitis. Two weeks prior to entry he was started on 50,000 unit tablets of penicillin and received his last dose nine days before entry. Three days before entry he ate fresh strawberries, to which he was accustomed. Forty-eight hours before entry he developed generalized urticaria, then swollen, red, stiff, painful, toes and fingers, followed by generalized edema of hands, feet, and ankles, and "marble-sized knots" on his scalp. During the forty-eight hours before entry he vomited repeatedly and became delirious and unmanageable. One local physician gave him three injections of adrenaline with only partial relief for three to four hours and another physician gave him 50 mg. of Benadryl every two hours for the twenty hours just prior to entry with little or no relief.

Past history revealed that he had received penicillin about two years prior to entry without reaction and had taken sulfonamides on several occasions without reaction. Family history was negative except that one aunt has had hay fever, hives, and asthma.

Physical examination on entry revealed an acutely ill, irritable, semi-delirious boy with generalized fiery red, circinate, raised urticarial lesions, generalized small, tender lymph nodes, edema of eyelids, hands, feet, and ankles, and inability to walk because of pain. His temperature was 102 ° F. rectally; pulse 138 per minute; respirations 28 per minute; blood pressure 108/68. Complete blood count was normal except for a white blood cell count of 11,350 with 87 per cent neutrophiles, of which 40 per cent were nonsegmented. Urinalysis after intravenous fluids was negative except for a trace of albumin and a trace of acetone. He was skin tested with procaine, given 48 mg. of sodium phenobarbital intramuscularly, and after thirty minutes a continuous drip of 250 c.c. of physiologic saline solution containing 250 mg. of procaine hydrochloride was started. By the end of forty-five minutes he was very restless and 32 mg. of sodium phenobarbital were given intramuscularly. By the end of one hour he was sleeping soundly and about 40 per cent of the urticaria

had disappeared. By the end of two hours all of the solution had been administered; the urticaria had decreased only about 40 per cent but he was still sleeping soundly. He had not slept for forty-eight hours prior to this, and after intravenous procaine he slept for ten hours, waking only two times for short periods. The next morning the urticaria had decreased by about 60 per cent but he still had some edema of his face, hands, and feet. During the following eight hours he continued to improve and was started on 50 mg. of Pyribenzamine every four hours and discharged after forty hours with only faint scattered urticaria and slight edema of his hands and feet. He was kept on decreasing doses of Pyribenzamine for one week.

CASE 6.*—J. L., a 3-year-old girl, was admitted to the emergency room of the North Carolina Baptist Hospital March 24, 1948, with a severe burn estimated by the surgical department as being 60 to 70 per cent of the body surface. Superficial débridement and a cut down were done under drop ether anesthesia. After recovering from anesthesia she was in severe pain and became unmanageable. Two hundred fifty cubic centimeters of 2.5 per cent glucose in 0.5 normal saline containing 250 mg. of procaine were started by slow drip in the cut down and given over a period of one and one-half hours. She was fairly quiet during the administration and for about five hours after completion of the infusion. No further intravenous procaine was given because of her need for plasma and other fluids. This patient has had no adverse reactions during six months of observation.

COMMENT

The proper dosage of intravenous procaine has not been determined. Allen[1] has used large doses in obstetrics and in surgical procedures with very little difficulty. For the relief of postoperative pain, he gave one patient two grains of sodium phenobarbital intramuscularly and followed this with an intravenous infusion of 10 Gm. of procaine hydrochloride in 800 c.c. of 5 per cent glucose in distilled water. This solution was given at an average rate of 3 c.c. per minute. When the rate of administration was speeded up to 8 c.c. per minute the patient complained of dizziness.

The number of injections of intravenous procaine that a patient can tolerate has not been determined. Allen[2] gave one patient twenty-five intravenous infusions of procaine in forty days for the relief of severe anginal attacks. This patient had no apparent injurious effects. There have been few animal experiments on this problem.

The length of effect of procaine is not known. Gordon[3] found that pain associated with burns was abolished for from six to twelve hours after the administration of the intravenous procaine. The fourth patient we treated received relief from pain and itching for from four to eight hours after the completion of the procaine infusion. Since procaine is hydrolyzed and detoxified by procainase in the blood stream a few minutes after injection,[4] it is difficult to explain the relief of pain for hours. The role of the breakdown products of procaine has not been determined.

State and Wangensteen[5] suggested several explanations for the action of procaine; namely, the direct action on cells, antiacetylcholine action, epinephrine potentiating action, and a possible antihistamine effect. The formulas

*Private patient of Dr. Felda Hightower, Department of Surgery, Bowman Gray School of Medicine, Winston-Salem, N. C.

for Benadryl, Pyribenzamine, and procaine are closely related structurally. All three drugs contain either an aminoethyl or an ethylene diamine group and procaine breaks down into diethylaminoethanol and para-aminobenzoic acid. Both Pyribenzamine and Benadryl counteract the spasmogenic effect of acetylcholine and all three drugs relieve phases of serum sickness. Benadryl and Pyribenzamine are effective in over 80 per cent of the cases of serum sickness in the relief of skin lesions such as urticaria.[6] Patients with joint involvement are not usually helped,[6] however, and intravenous procaine may be of value.

Early toxic symptoms observed in the use of intravenous procaine are numbness, nausea, and dizziness. If any of these symptoms develops, the rate of administration should be decreased. If further evidences of toxicity such as restlessness and irritability appear, the drip should be discontinued and sodium phenobarbital should be given intramuscularly. Convulsions and respiratory failure have been attributed to the local use of procaine but have not been encountered in slow intravenous drip administration. Intravenous Sodium Amytal may be given to control convulsions and artificial respiration administered in the event of respiratory depression. One author[4] has reported the use of intravenous procaine in 2,000 patients without ill effect.

Procaine probably should not be administered to patients (1) who are hypersensitive by skin test, (2) who have extensive liver damage, (3) who suffer from myasthenia gravis, (4) who have epilepsy or family history of epilepsy, or (5) who have a history of recent head injury.[7] Procaine is probably not contraindicated in patients receiving sulfonamides.[8]

SUGGESTED TREATMENT SCHEDULE

General factors of dosage which should be considered in the administration of intravenous procaine are: concentration of procaine, quantity of fluid, rate of administration, and duration of administration. An arbitrary dosage schedule and procedure for children have been devised:

1. Skin test with 0.1 per cent procaine hydrochloride.
2. Appropriate dosage of phenobarbital twenty minutes before starting intravenous procaine.
3. Procaine hydrochloride dissolved in either physiologic saline or 5 per cent glucose in water so as to give a 0.1 per cent solution.
4. Intravenous administration by slow drip (twenty to thirty drops per minute) over a period of at least two hours.
5. Repeat in eight hours if necessary.
6. Have on hand Sodium Amytal for intravenous use in case of excessive central nervous system stimulation.
7. Amount of fluid according to age:
   2 to 5 years—125 to 250 c.c. of 0.1 per cent procaine solution.
   5 to 10 years—250 to 500 c.c. of 0.1 per cent procaine solution.
   10 to 15 years—500 to 750 c.c. of 0.1 per cent procaine solution.

SUMMARY AND CONCLUSIONS

Six children were given intravenous procaine for the relief of symptoms. Five had serum sickness or a related allergic disorder and one was suffering extreme pain from an extensive burn. A treatment schedule for children is presented.

Patients who have severe manifestations of serum sickness such as myalgia and arthralgia and who are not relieved by the so-called "antihistaminics" may benefit from the use of intravenous procaine. Patients with other painful conditions, particularly those with capillary damage as in extensive burns, may receive symptomatic relief.

I wish to express my appreciation to Drs. David Greer, Byron York, and George Salmon of Houston, Texas, and Dr. Felda Hightower of Winston-Salem, N. C., for permission to include case histories of their patients in this paper.

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METHYL TESTOSTERONE IN THE TREATMENT OF PREMATURE INFANTS

JANET HARDY, M.D., AND LAWSON WILKINS, M.D.
BALTIMORE, MD.

A PRELIMINARY report by Shelton and Varden[1] suggested that the administration of testosterone preparations to premature infants was of value in decreasing the expected mortality rate of infants weighing less than 2,000 Gm. at birth and that, by promoting a more satisfactory weight curve, it decreased the period of hospitalization necessary for each infant. A subsequent more complete report[2] tends to confirm these impressions. No untoward effects of the drug were noted by the authors.

It is generally accepted that the administration of methyl testosterone to an individual brings about an increase in nitrogen retention, protein anabolism, and tissue growth.[3] Therefore, it seems reasonable to hope that the administration of this substance to premature infants might be of value in promoting growth as measured by gain in body weight.

An effort to determine if testosterone is of practical value in this respect was made between May and November of 1947 in the Nursery Unit for Premature Infants in the Harriet Lane Home, The Johns Hopkins Hospital. Alternate premature infants were given methyl testosterone by mouth twice daily, 2.5 mg. emulsified in 5 c.c. of sterile water and given by medicine dropper or gavage tube immediately before feeding. In all except two patients the treatment was begun on the seventh to tenth day of life. In patient A (Chart 1) it was begun at 11 weeks and in patient H at 6 weeks. The medication was continued for four weeks. In most instances it was withdrawn abruptly, but in some the dose was reduced to 2.5 mg. daily for an additional three days and then discontinued.

The infants receiving methyl testosterone and those serving as controls were all handled according to the standard nursery regime. Feedings consisted of half-skimmed milk with 10 per cent added carbohydrate, having a caloric value of one calorie per cubic centimeter of formula. After the tenth day of life 120 to 130 calories per kilogram of body weight were fed daily. Supplementary vitamins A, C, and D were started on the fifth or sixth day of life.

In all, twenty-six infants, varying from approximately 900 to 1,900 Gm. at birth, were given methyl testosterone as described above. Their response to therapy as measured by computing the average daily weight gain for the total period of hospitalization (including the period of initial weight loss) was compared with that of the control, untreated group. The results of this comparison may be seen in Table I. In order that a graphic representation might be made, a group of infants of varying birth weight was chosen from the testosterone-

From the Department of Pediatrics, Johns Hopkins University School of Medicine, and the Harriet Lane Home of the Johns Hopkins Hospital.

treated group and paired off with an untreated infant of the same sex and race, of approximately the same birth weight. The selection was done by an individual who had no knowledge of the clinical course of the infants in either group.

In addition, six infants weighing between 850 and 1,370 Gm. at birth were each given 4 mg. testosterone proprionate in oil intramuscularly, on the first day of life and every third day thereafter. All six died between the second and tenth days of life and are not included in this study.

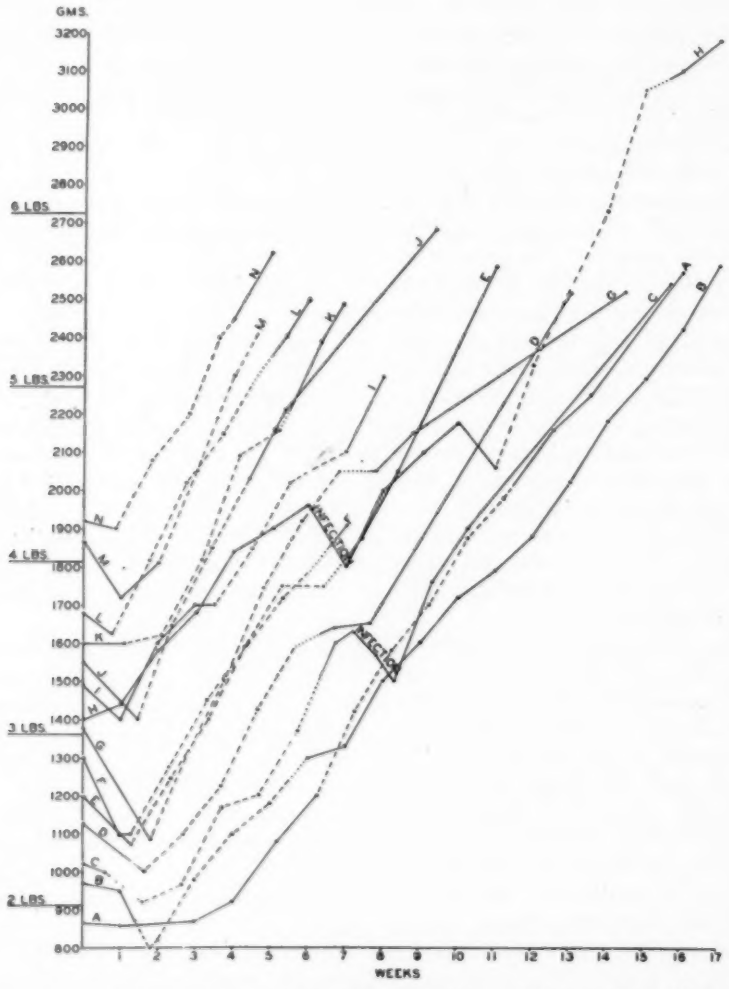

Chart 1.—Weight curves of premature infants receiving methyl testosterone 2.5 mg. twice daily given during the period marked by broken line; 2.5 mg. once daily during the period marked by dotted line. No therapy during period marked by solid line.

TABLE I

BIRTH WEIGHT (GM.)	NO.	2.5 MG. METHYL TESTOSTERONE TWICE DAILY (AVERAGE DAILY GAIN IN GM.)	NO.	CONTROL (AVERAGE DAILY GAIN IN GM.)
800- 990	2	15.5	2	15.6
1,000-1,199	5	16.3	5	17.3
1,200-1,399	4	15.7	6	17.6
1,400-1,599	6	17.4	4	16.5
1,600-1,799	5	17.9	3	19.5
1,800-1,999	2	21.7	6	20.6
2,000-2,199	2	15.1	0	
Totals	26	17.0	26	18.2

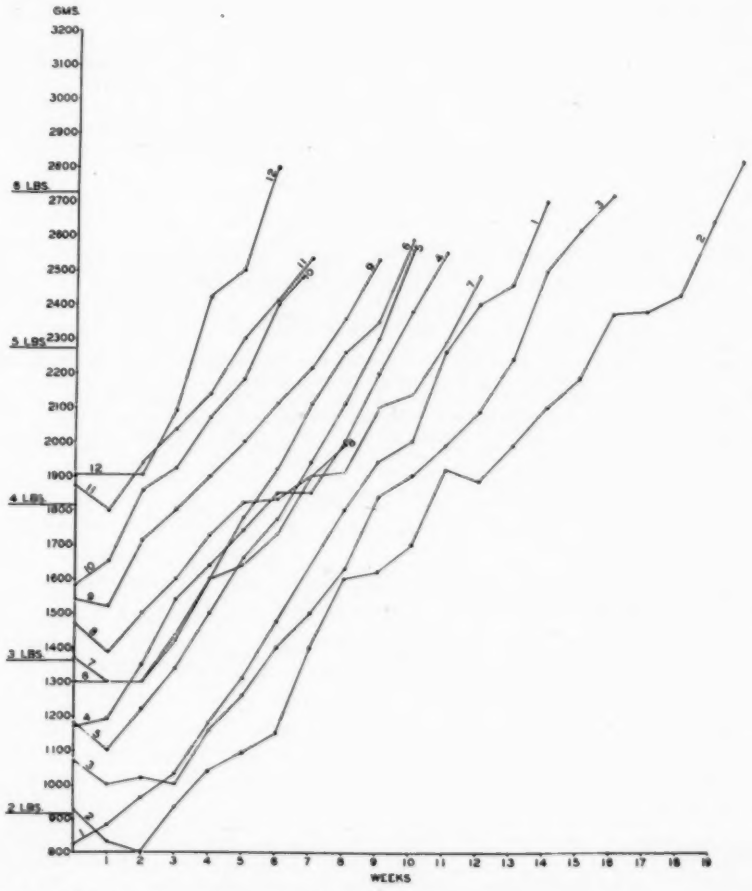

Chart 2.—Weight curves of premature infants raised on same general regime as those in Chart 1 but given no testosterone.

RESULTS

As may be seen by comparison of the graphic charts, there is no significant difference in the weight curves of the infants treated with methyl testosterone and those who did not receive the drug. Furthermore, as shown in Table I, the average daily weight gain of 17 Gm. made by the infants treated with testosterone is not significantly different from an average daily weight gain of 18.2 Gm. in the control group.

The only child in whom any dramatic effect was observed was patient H (Chart 1), who did not receive the drug until he was 10 weeks of age. This was a twin who had failed to gain at the expected rate. He gained rapidly during the period of treatment but continued to do so after the drug was withdrawn.

No untoward effects of the medication were noted. Two of the male infants showed moderate enlargement of the penis, which has persisted. Several of the girls showed transient enlargement of the elitoris.

It is of interest that in very few instances was weight loss observed at the termination of the testosterone therapy, whereas in older patients having increased protein anabolism with testosterone, a transient loss of weight and nitrogen usually occurs on its withdrawal. This suggests that the drug had had no marked effect in increasing nitrogen retention.

CONCLUSION

In the clinical experiment described above, no benefit was observed from the use of methyl testosterone in the treatment of premature infants.

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CARBOHYDRATE SUPPLEMENTS (LACTOSE AND STARCH HYDROLYSATES) IN INFANT FEEDING

Blood Sugar Changes Following the Administration of Carbohydrate Supplements in Various Milk Media

Samuel Natelson, Ph.D., Marvin Sherman, B.S., and Benjamin Kramer, M.D.
Brooklyn, N. Y.

THESE studies were initiated in an attempt to evaluate carbohydrate supplements in infant feeding for the neonatal period by the classical, statistical approach. Our failure to obtain convincing results by this method in 1,227 cases led us to use blood sugar tolerance curves for this purpose. By the latter method it was found that the addition of lactose to heated milk formulas produced, in the infant, sugar tolerance curves different from those obtained by feeding lactose in raw milk formulas.

The high carbohydrate requirement of infants has been emphasized by Heymann.[1] He pointed out that in infants hypoglycemia is easily induced by carbohydrate starvation, the glycogen reserves of the liver are low, and the carbohydrates are of importance in water retention. It also has been said by Winter[2] that the normal fasting blood sugar levels are low in infants, probably due to the poor ability to absorb foods in general.

The lack of agreement in the literature on studies where growth curves were used as a criterion of the nutritional value of a carbohydrate led us to question this as a sole method of evaluating a feeding formula. The number of cases used in many of these studies seemed to us, merely from a cursory inspection, to be too small to warrant the conclusions drawn. This objection could be met in one of two ways. One method would be to carry out the study on large numbers of carefully controlled cases. The other alternative would mean the setting up of our experiments in such a way that a specific biologic effect would be studied.

We decided to test the first method by finding out how many cases would be necessary to establish average growth curves on basic hospital formulas. The basic formula used in this hospital consists of one part evaporated milk, two parts sterile water, and 5 per cent added carbohydrate. Both Cartose* and Dextri-Maltose† were used as the added carbohydrate in this study. Breast-fed infants who, in addition, received basic Cartose and Dextri-Maltose formulas "post cibum" also were studied. Growth curves were drawn for each infant for the first seven days of life. This arbitrary period was necessarily chosen since many infants left the hospital after the seventh day.

From the Pediatric Research Laboratory and the Department of Pediatrics of The Jewish Hospital of Brooklyn.

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*Cartose is manufactured by the Winthrop-Stearns Co.

†Dextri-maltose is manufactured by Mead Johnson and Co.

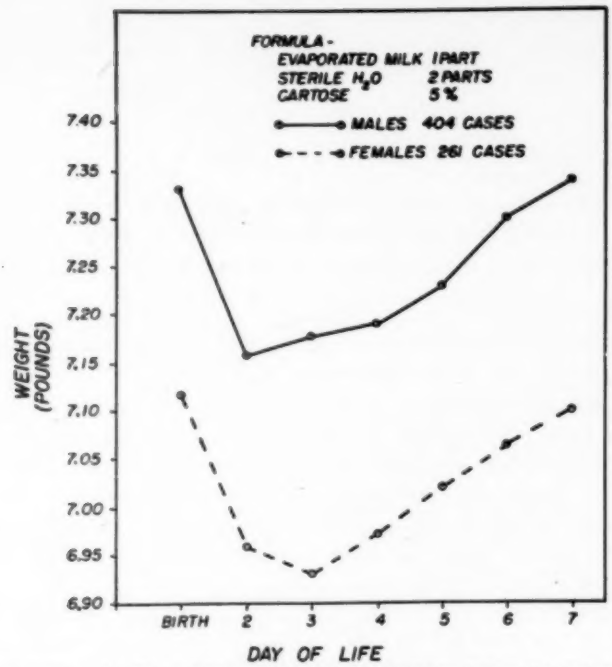

Fig. 1.—Average curve for the weight change of normal infants during the first seven days of life on evaporated milk formula plus Cartose.

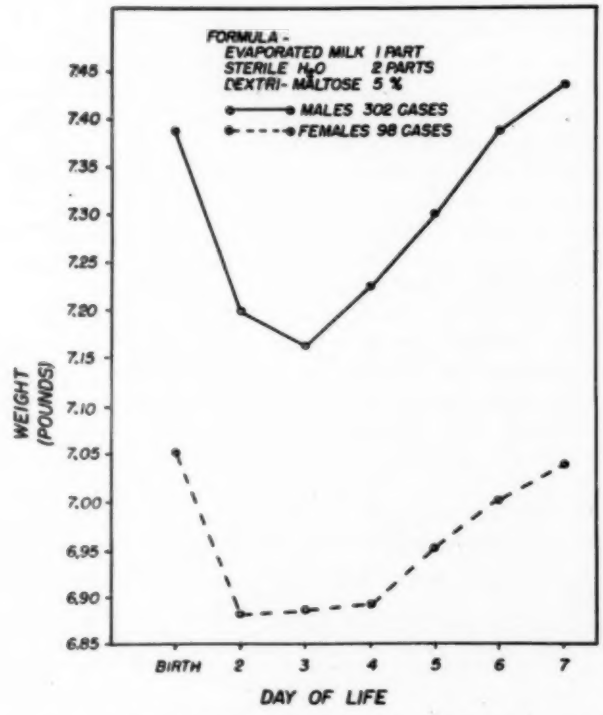

Fig. 2.—Average curve for the weight change of normal infants during the first seven days of life on evaporated milk formula plus Dextri-Maltose.

TABLE I. NET DIFFERENCE BETWEEN BIRTH WEIGHT AND WEIGHT AT SEVEN DAYS IN RELATION TO THE TYPE OF FEEDING

FORMULA	SEX	NO. CASES	AVERAGE BIRTH WEIGHT (LB.)	AVERAGE WEIGHT AT 7 DAYS (LB.)	NET CHANGE (%)
Evaporated milk with 5 per cent Cartose	M	404	7.33	7.36	+0.41
	F	261	7.12	7.10	-0.28
Evaporated milk with 5 per cent Dextri-Maltose	M	302	7.39	7.44	+0.68
	F	98	7.05	7.04	-0.14
Breast milk with Cartose formula or Dextri-Maltose formula "posteibum"	M	86	7.34	7.34	0.00
	F	76	7.17	7.12	-0.70

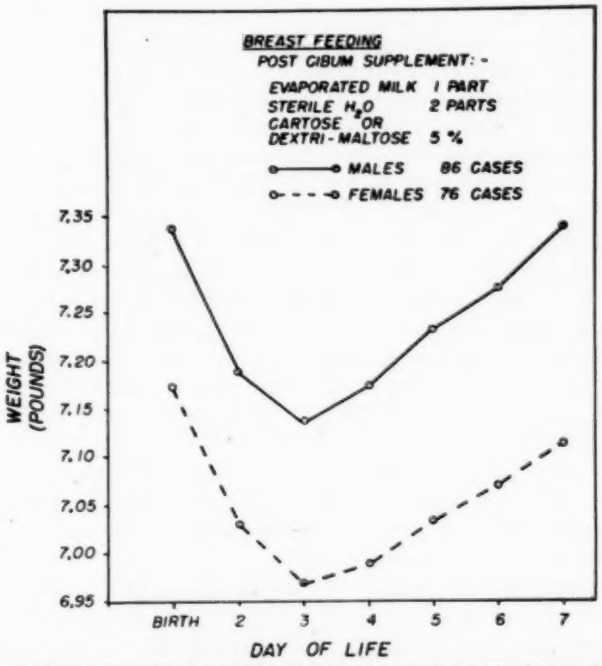

Fig. 3.—Average curve for the weight change of normal infants during the first seven days of life on breast feeding supplemented with evaporated milk formula plus starch hydrolysate.

For each formula group the daily weights were tabulated and averaged. Each point on the accompanying graphs (Figs. 1, 2, and 3), therefore, represents the average weight of all infants in a particular group on the day under consideration.

Table I expresses the net change in weight at the end of seven days as a percentage of the birth weight in a total of 1,227 infants.

Having found the statistical weight curve method tedious, depending upon the reliability of a large number of nurses, and time-consuming, with a

minimum of results, we decided to attempt a more objective method. For preliminary investigation it was decided to use the blood sugar tolerance curve.

The procedure used in the tolerance tests was as follows: The blood used was capillary blood taken from the infant's heel by needle prick. The fasting specimen was drawn at least three and one-half hours after the preceding feeding. Subsequent specimens were drawn thirty, sixty, and one hundred twenty minutes after completion of the test feeding. The bloods were analyzed for sugar content by a modification of the Folin-Wu method[3] further modified by us to employ 0.02 ml. of whole blood measured in a Sahli hemoglobinometer pipette, and the final color read by the Klett-Summerson photoelectric colorimeter.

The infants used in this study were normal, full-term infants born on the general obstetrical service of our hospital. All the infants were housed in the same nursery and received the same nursing care. Only healthy infants who weighed at least 5 pounds 10 ounces, but not more than 8 pounds were chosen for this study. The routine used in feeding in our hospital is as follows: Immediately after birth the infant is brought to the nursery, washed, and weighed. No liquid is given by mouth for the first eight hours of life. At the end of this eight-hour period, one-half ounce of glucose solution is given by mouth. Four hours after this one-half ounce of the stock hospital formula is given, and every four hours subsequently the infant is fed one-half ounce per feeding on the first day, and the amount is increased by one-half ounce on each succeeding day; that is, one ounce on the second day, 1½ ounces on the third day, 2 ounces on the fourth day, etc., until a maximum of 3 ounces per feeding is reached. In all of the following studies, the "first test day" is the third day of life and the "second test day" is the fourth day of life.

The formula used was the stock hospital formula with 5 per cent of the carbohydrate to be tested added. The volume administered at each test period was 2.0 ounces. The formulas were analyzed after being made up so that the carbohydrate content was the same in all.

In order to limit the number of determinations to a reasonable quantity and at the same time have our results be significant, we ran a series of studies for two successive days, comparing the reproducibility of the sugar tolerance curve in the same infant. The formula used was the stock hospital formula with 5 per cent added Cartose.* The results are shown in the average curves in Fig. 4.

It is evident from the foregoing results that the average glucose tolerance curves of the same infants on the third and fourth days of life showed enough similarity to justify a comparative study based on this criterion.

*The carbohydrate chosen for this study was Cartose. It is a sterile, easily soluble sugar which contains no salt or other added ingredients which might interfere with the study. Cartose is a pale amber syrup containing 77 per cent solids. One ounce by volume of the liquid is approximately equal to one ounce by weight of a powdered carbohydrate. One liquid ounce or two tablespoonfuls is equivalent to 120 calories. This would be equivalent to four tablespoonfuls of a powdered carbohydrate. Cartose is an hydrolysate of corn starch and contains no added sugar. Unlike Karo, the hydrolysis is controlled to produce a higher percentage of dextrins and maltose. Cartose is composed of approximately 36 per cent dextrins, 20 per cent malto-dextrins, 21 per cent maltose, and 23 per cent glucose. It has been found by Krost[7] to be a perfectly safe and well-utilized carbohydrate.

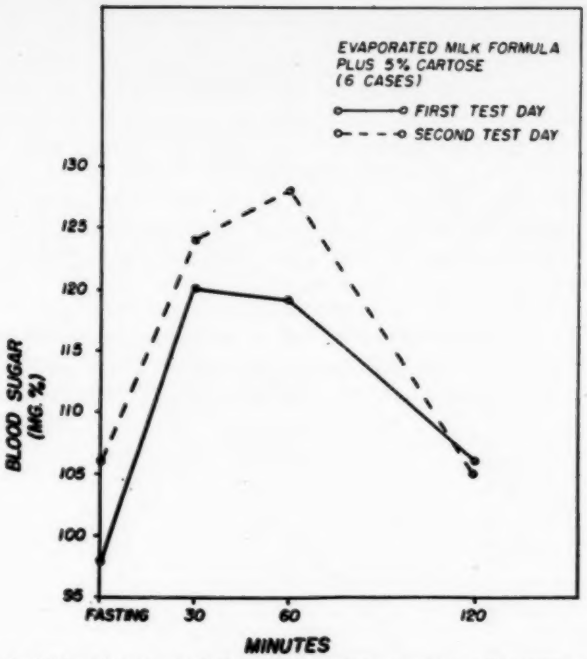

Fig. 4.—Reproducibility of average blood sugar tolerance curves on the same normal infants on succeeding days.

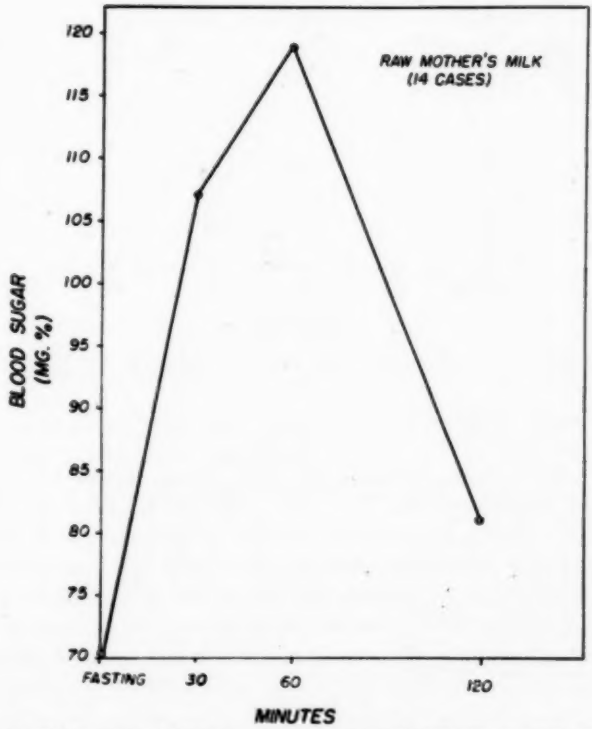

Fig. 5.—Average blood sugar tolerance curve for normal infants on raw mother's milk (approximately 7 per cent lactose content).

Lactose had been reported as producing tolerance curves with low peaks as compared to starch hydrolysates.[5] We, therefore, examined the blood sugar tolerance curves of fourteen infants using 2.0 ounces of raw mother's milk fed by bottle.* This milk contained approximately 7 per cent lactose. In this study we obtained curves with high peaks which returned almost to the fasting level within two hours in each case. The average curve for these cases is shown in Fig. 5.

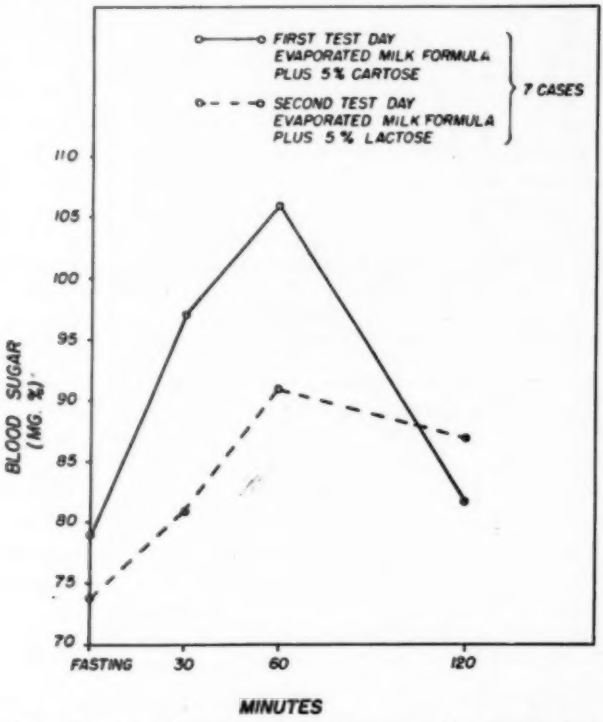

Fig. 6.—Comparison of average blood sugar tolerance curves for normal infants on starch hydrolysate and lactose administered in evaporated milk formula.

Experiments reported in the literature had been performed by dissolving the lactose in water. We considered the possibility that these experiments might not apply to milk formulas, for the medium in which the lactose was administered might have some bearing on the results obtained. To test this factor we ran a study using evaporated milk formulas on both test days, but using a 5 per cent Cartose supplement on the first test day and a 5 per cent lactose supplement on the second test day on the same infant. Fig. 6 shows the results on seven infants tested in this way.

*Raw mother's milk was obtained from the Mothers' Milk Bureau of the Children's Welfare Federation of New York City.

Our results confirmed the fact that lactose produces curves with lower peaks which do not return to the fasting level in two hours when employed in the blood sugar tolerance test. Nevertheless, mother's milk containing 7 per cent lactose had produced tolerance curves with high peaks which had returned to almost the fasting level at the end of two hours.

Obviously, there was a distinction between evaporated cow's milk and mother's milk in influencing the shape of the sugar tolerance curve. We felt that this difference might be in the different treatments to which the milks had been subjected, rather than the species of milk used. We decided to compare the tolerance curves produced by lactose in raw cow's milk with those produced by lactose in evaporated cow's milk.

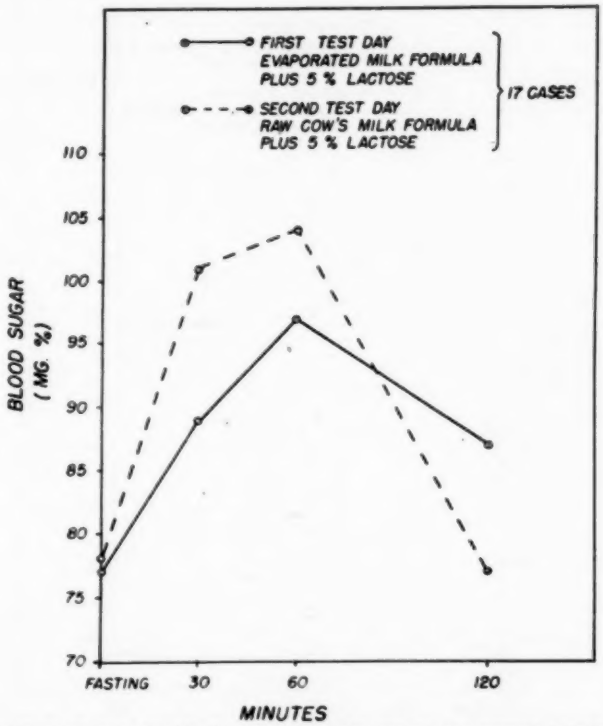

Fig. 7.—Comparison of average blood sugar tolerance curves for normal infants on lactose administered in evaporated milk formula and raw cow's milk formula.

In this study we avoided the use of heated mother's milk, for in our experiments we found that rapid changes take place in mother's milk even on standing at reduced temperatures, as measured by rapid loss of phosphatase activity. We chose the more stable certified raw cow's milk as representing unchanged cow's milk.* We carefully checked the phosphatase activity of this milk by the Scharer method[6] to ensure that it had not been pasteurized

*The raw cow's milk used was Walker Gordon Certified Raw Cow's Milk.

previously, and compared it against the standard hospital formula. The raw milk contained approximately 1,000 Scharer units per milliliter whereas the hospital formula contained no phosphatase activity, as would be expected.

In a series of seventeen infants we compared the blood sugar tolerance curves obtained with evaporated milk formula (1 part evaporated milk to 2 parts of water) with 5 per cent lactose supplement, and with raw cow's milk formula (2 parts raw milk to 1 part of water) with 5 per cent lactose supplement. From Fig. 7 it is apparent that the sugar tolerance curve of the raw cow's milk formula resembles more closely the sugar tolerance curve obtained with raw mother's milk than does the curve obtained with the evaporated milk formula.

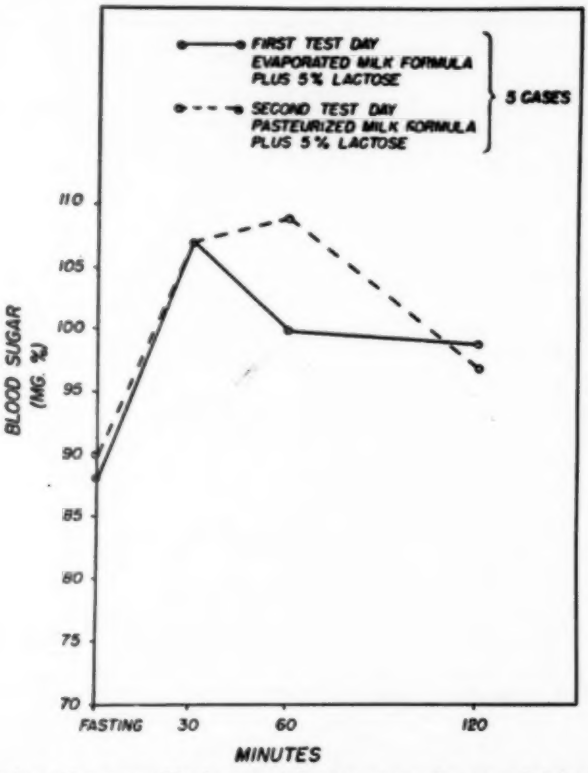

Fig. 8.—Comparison of average blood sugar tolerance curves for normal infants on lactose administered in evaporated milk formula and pasteurized milk formula.

Thus, our observation that lactose produced sugar tolerance curves with low peaks was again confirmed when lactose was fed in an evaporated milk mixture. However, when lactose was administered in raw milk, the blood sugar tolerance curve assumed the general shape of that produced by the monosaccharides and that produced by lactose in raw mother's milk. Lactose

with raw cow's milk was given on the second test day to the same infant to avoid possible changes in the intestinal flora due to the administration of a raw milk. The results are valid, for lactose, whether given on the first or second test day, showed similar tolerance curves (see Fig. 6). Also our controls (see Fig. 4) showed little variation from first to second test day on the same infant.

The question was raised as to whether it was valid to compare the effects of evaporated milk and raw cow's milk since they were physically dissimilar due to the treatment of the evaporated milk. Therefore, we extended the study to the comparison of the sugar tolerance curves produced by lactose in evaporated milk formula (one part evaporated milk, two parts water, 5 per cent lactose supplement) to that produced by lactose in whole pasteurized milk formula (2 parts whole pasteurized milk, 1 part water, 5 per cent lactose supplement). Fig. 8 indicates that little difference exists in this respect between pasteurized and evaporated milk.

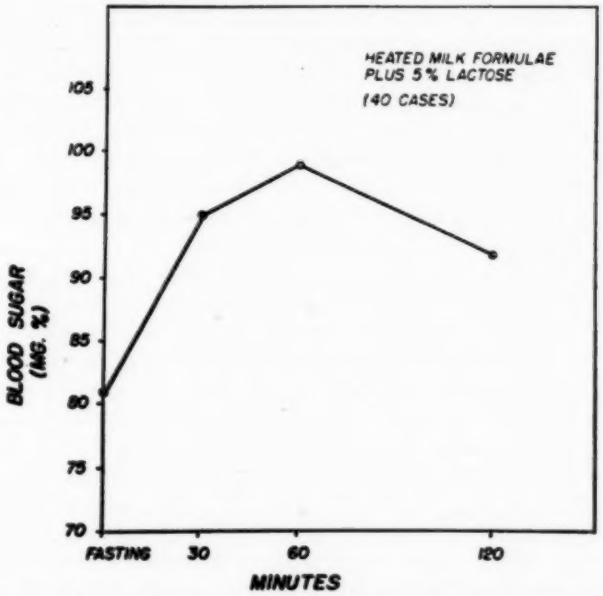

Fig. 9.—Average blood sugar tolerance curve for forty normal infants on lactose administered in heated cow's milk formulae.

In the curves above, thirty-four individual tolerances are reported using lactose added to treated milk formulas. In addition, we have performed six additional tolerances using lactose in evaporated milk, not reported herein. Thus we have carried out forty blood sugar tolerances using lactose in treated milks. This number appears large enough to warrant the conclusion that lactose will produce tolerance curves with low peaks and slow return to the fasting level as shown in Fig. 9.

DISCUSSION

From Figs. 1, 2, and 3 it is evident that the characteristic growth curve in the neonatal period does not differ appreciably among the three groups of infants observed. The greatest loss of weight occurred during the first twenty-four hours. This was followed by a lesser weight loss, no weight loss, or a slight gain during the next twenty-four hours. Thereafter there was a steady gain throughout the period of observation. Thus, the statistical minimum weight occurred on the third day of life (taking the day of birth as the first day of life).

Table I indicates that the average birth weight of male infants was greater than that of female infants. This is in agreement with observations previously reported.[7] Further, the net change in the weight of male infants at the end of seven days, expressed as a percentage of the birth weight, was algebraically greater than that of female infants. No statistically significant difference in net change from birth weight was observed among the three groups. The breast-fed infants with feedings supplemented with evaporated milk formulas did not have a sufficiently large representation for comparison with the other two formulas. The "post cibum" feeding used was the basic hospital formula (1 part evaporated milk and 2 parts sterile water) supplemented with either 5 per cent Cartose or 5 per cent Dextri-Maltose. The weight statistics of all breast-fed infants were pooled to obtain the figures in Table I. This was done in making up the table because the results obtained comparing the two carbohydrate supplements in evaporated milk formulas indicated no significant differences between the two.

The breast-fed group was drawn mainly from the general obstetrical service nursery of the hospital. This was necessary because of the fact that a very small percentage of the mothers on private service breast feed their children. Thus this group of breast-fed infants represents essentially a group in a less privileged financial status.

We noted that the average growth curve of the first thirty male infants on basic hospital formula with Cartose supplement showed a marked net gain at the end of seven days. But when these figures were averaged together with the entire series, there was shown a much lower net gain for the seven-day period. When approximately one-half the total number of cases had been tabulated (532 cases), examination of the net change in weight at the end of seven days indicated that the breast milk feeding supplemented with starch hydrolysates was superior to Cartose in evaporated milk formula, which in turn was superior to Dextri-Maltose formula (Table II). On final tabulation (Table I) the reverse order was observed.

These observations indicate the inherent danger of drawing conclusions from averages of a short series in this type of study. The number of cases for a proper study of this type should run into many thousands, and we decided that it would be uneconomical from our point of view.

It may be noted that in this study no difference was observed in the conditions of the stools, buttocks, or general well-being of any of the infants on the three different formulas.

TABLE II. NET DIFFERENCE BETWEEN BIRTH WEIGHT AND WEIGHT AT SEVEN DAYS IN RELATION TO THE TYPE OF FEEDING AT MIDPOINT OF STUDY (532 CASES)

FORMULA	SEX	NO. CASES	AVERAGE BIRTH WEIGHT	PER CENT CHANGE AT 7 DAYS
Evaporated milk with 5 per cent Cartose	M	170	7.362	-0.42
	F	152	7.177	-0.98
Evaporated milk with 5 per cent Dextri-Maltose	M	37	7.456	-0.62
	F	51	7.101	-1.21
Breast milk supplemented with Cartose or Dextri-Maltose formula	M	61	7.357	+0.27
	F	61	7.205	-0.78

A study comparing different milk formulas by means of sugar tolerance curves on the same infant on succeeding days seems to be a more useful tool than the method of statistical growth curves. Fig. 4 indicates that even in a group as small as six infants reproducibility may be obtained from one day to the next using the same formula. This method, therefore, allows one to use the same infant, employed to test the formula, as a control.

The natural lactose found in mother's milk produced a blood sugar tolerance curve with a peak rise of approximately 50 mg. per cent higher than the fasting level as shown in Fig. 5. Further, the blood sugar level returned almost to the fasting level at the end of a two-hour period. Assuming that milk from a healthy mother is the ideal feeding for the infant, this curve can be taken as a criterion which should be duplicated when feeding an artificial milk formula.

In Fig. 6 it is seen that the lactose curve showed a peak rise of 18 mg. per cent over the fasting level. Moreover, the return to fasting level was delayed, the final level at the end of two hours still remaining at a much higher percentage of the peak level than the final level shown by the mother's milk (see Fig. 5). On this same chart (Fig. 6), the starch hydrolysate produced a curve approximating the shape of that produced by mother's milk, with a rise of 27 mg. per cent above the fasting level, but a closer return to the fasting level at the end of two hours.

The curve produced by raw mother's milk or by starch hydrolysate in evaporated milk could be approximated, however, when lactose was administered in raw cow's milk as shown in Fig. 7. Because of the importance of this finding, we extended this study to seventeen cases (thirty-four tolerance studies in all). Here, again, lactose produced lower peaks and a slower return to fasting level when administered in evaporated milk formula.

Fig. 8 illustrates a short study done on five cases (ten sugar tolerances) to see whether evaporated milk had some peculiarity in which it differed from pasteurized milk. It is evident even in this short series that there is no significant difference between the two milks in so far as the tolerance curves with lactose are concerned. The peak rise for evaporated milk was almost identical with that produced by pasteurized whole milk, being approximately 19 mg. per cent in both cases. In both cases, the blood sugar level returned to approximately 50 per cent of the peak rise at the end of two hours. This is distinct from lactose in raw mother's milk, where the drop was 80 per cent

of the peak rise, and lactose in raw cow's milk, where the drop was approximately 100 per cent of the peak rise at the end of two hours (see Figs. 5 and 7).

The blood sugar tolerance curve produced by starch hydrolysate in evaporated milk formula resembles that produced by lactose in raw cow's milk (see Figs. 6 and 7).

That lactose will produce its own characteristic tolerance curve when administered in heated cow's milk formulas is firmly established by the summary of the forty cases shown in Fig. 9. This is in agreement with the findings with lactose administered in water (ten cases) reported by Schlutz and collaborators.[5]

It is evident from our results that there is some ingredient or factor in raw cow's milk that will enable lactose to produce a sugar tolerance curve resembling that produced by raw mother's milk. This is not present in evaporated milk or in milk which has been pasteurized to the extent that the phosphatase activity has been destroyed. There are at least two hypotheses possible. One is that an enzyme is present in raw milk which aids in the splitting and/or the absorption of lactose by the intestinal tract. The other hypothesis is that the heating in the process of pasteurization may produce a change of the physical state of the mixture which interferes with absorption.

The ideal formula for a newborn mammal would most likely approximate the natural milk of that species. It is well known that the carbohydrate in human milk is lactose. The nutritional value and the side-effects of lactose have been studied in infants.[8-11] Several investigators[12-14] have studied the effect of alpha-lactose and beta-lactose upon the state of the intestinal flora and fecal conditions, indicating that lactose seems to be necessary for the normal growth of *Lactobacillus bifidus* in the intestine. Schimansky stated that the conversion of beta-lactose to the alpha-isomer is a function of the intestinal wall.[14] Malyoth[13] has found that intestinal *L. bifidus* cultures are formed in a shorter time and in greater purity after feeding infants beta-lactose than after mother's milk. The relation of lactose to fat metabolism has been emphasized by several investigators.[15, 16] Lactose supplies not only glucose but galactose. The function of the latter in normal human metabolism has not been clarified. Galactose is known to occur in cerebrosides and kerasin.

Thus it appears that there should be several advantages to the use of lactose in the diet of the infant. Our observations would imply that the medium in which the lactose is administered should have an important bearing on the relative value of this carbohydrate supplement. In the rat, both beta-lactose and the alpha-isomer are absorbed from the intestine at the same rate, and both produce undesirable effects such as alopecia, growth failure, and diarrhea.[17, 18] It would be of interest to see what the effects would be if the lactose were administered in raw milk.

The findings that raw milk produced different sugar tolerance curves than the heated milks may be in some way related to the observations of several investigators that there is better growth on raw mother's milk than on heated

mother's milk.[19-21] A few experimental observations are reported in the literature which show no difference between the two or a slight advantage for heated mother's milk.[22, 23] This latter group, when closely examined, is shown to consist of experiments with small numbers of infants over relatively short periods of time. For example, Kayser showed only seven cases with a slight advantage for heated milk.[22] His measure was weight gain. In view of the above observations that such studies are invalid unless large numbers of cases are used, the results of his study are in question. Kujath[23] studied twenty-nine infants, of whom ten subsequently died, six received heated, and 4 received raw milk. The remaining nineteen was too small a number upon which to draw conclusions, although a slight favor for unheated mother's milk was shown. Ladd and collaborators[24] claim advantages for raw cow's milk over pasteurized milk. Our growth studies should not be compared with the studies referred to above. Our statistical studies extended over a seven-day period only, while the studies referred to concern themselves with growth for longer periods of time.

In our study we took the phosphatase activity of raw milk as the criterion of its unchanged condition. We found that untreated mother's milk taken at a collecting station early in the morning and delivered to us at noon had already lost a great deal of its phosphatase activity. Upon analysis, the mother's milk was found to contain from 36 to 43 Scharer units per milliliter, whereas the phosphatase values in raw cow's milk run about 1,000 Scharer units per milliliter. It was also observed that there was a physical change in mother's milk on handling. Milk obtained from the collecting center after having been packaged and delivered by messenger, when allowed to stand in the refrigerator overnight, appeared as though the fat had been churned into butter. If milk is administered in this form, with the colloidal state disturbed, there is a probable reduced absorbability of fats.[25]

Recently, while the present study was in progress, a publication appeared[26] in which the conclusion was reached that artificial cow's milk formulas produced better growth in premature infants than mother's milk. Close examination of this publication shows that it involved 122 infants, of whom sixteen were on mother's milk. Weight changes were used as an index of the value of the formula. Examination of the substance which was called "mother's milk" showed that it was quite remote from the mother's milk that issues from the breast. These investigators boiled the milk for five minutes. The milk would then fall into the category of a pasteurized milk in which the ingredients necessary for proper utilization of lactose may be destroyed. Second, no B-complex vitamins were added to the milk to make up for the vitamins destroyed in the boiling treatment. Third, the milk was strained after boiling, which removed at least some of the proteins and fat, thus removing it from the category of whole milk. From our observations in handling mother's milk, we feel that this sort of treatment tends to coagulate the fats into larger globules. It has been observed that the nature of the dispersion and the particle size are important considerations in the absorption of the fat-soluble vitamins.[27, 28] The breaking of the natural milk emulsion

probably results in an interference with the absorption of fats and fat-soluble vitamins.

Any study comparing mother's milk with an artificial formula can be made only by feeding the infant at the breast and weighing him before and after feeding, unless proper precautions are taken to preserve the original character of the milk. Several studies of this type have appeared in the literature, particularly the series of studies by Catel.[21, 29, 30] He found in a large series of premature infants that untreated mother's milk was superior to pasteurized mother's milk, and that there was better growth and lessened mortality. He also found that freezing raw mother's milk was a satisfactory method of preservation as opposed to pasteurization.[31] Freezing the milk does not destroy the enzymes or the vitamins, nor does it affect its digestibility for the premature infant. It must be pointed out that pasteurization does not destroy all the enzymes of raw milk. For example, it does not destroy the catalase or reductase.[32]

CONCLUSIONS

1. Growth studies on 1,227 infants for the first seven days of life, fed on evaporated milk formulas supplemented with starch hydrolysates, and breast-fed infants who received a supplement formula, were carried out.

2. No significant differences were demonstrated between the two different starch hydrolysates (Cartose and Dextri-Maltose) and breast feeding, using the statistical growth curve as a criterion.

3. The same infant on two successive days shows a fairly close correlation in blood sugar tolerance curves using the same formula feeding on both days, and this procedure may be used as a test for comparing various carbohydrates.

4. Raw mother's milk (containing 7 per cent lactose) produces a sugar tolerance curve characterized by a relatively high peak and a return to almost the fasting level at the end of two hours.

5. Sugar tolerance curves obtained when lactose is administered in evaporated or pasteurized milk formulas show relatively low peaks and a delayed return to the fasting level.

6. Lactose, when administered in raw cow's milk formula, exhibits a sugar tolerance curve which resembles more closely that produced by using raw mother's milk than that produced by using lactose in heated cow's milk formulas.

7. Starch hydrolysates, when administered in evaporated milk formula, produce sugar tolerance curves which resemble those produced by lactose in raw cow's milk formula.

8. These results would imply that a factor is present in raw milk which is destroyed on heating and which will influence the shape of the tolerance curve obtained with lactose when administered to newborn infants.

9. The disappearance of this factor must not be interpreted as signifying that raw milk is superior in nutritional value to artificial milk formulas. Further investigation is needed in this direction. Our statistical studies have revealed no difference in nutritional value between breast milk and artificial formulas.

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FUNGUS STUDIES IN ATOPIC DERMATITIS

Failure to Demonstrate Pathogenic Fungi in the Lesions

Henry Harris Perlman, M.D., Philadelphia, Pa.
With the Technical Assistance of
Dorothy Furman, Frances E. Karpluk, and Grace Anderson
New York, N. Y.

IN examination of infants and children suffering from atopic dermatitis, physicians are bound to encounter lesions which in clinical appearance suggest a superficial fungus infection, that is to say, lesions which are not numerous, are roughly and sharply circumscribed with scaling and an apparent tendency to clearing in the center. Indeed, in the absence of any positive history of atopy in the patient's family and failing the signs of a true atopic dermatitis in such regions of the body as the antecubital and popliteal spaces, one sometimes must consider mycotic infection in differential diagnosis. Therefore, it has seemed worth while to employ modern methods once again to ascertain whether pathogenic fungi or immunologic evidence of fungus infection could be found in a series of cases of atopic dermatitis.

It is generally accepted that fungous infection is not an etiologic factor in producing the lesions of atopic dermatitis. However, a few studies have been conducted to test the moot point whether fungi play any active part in the causation of so-called infantile eczema. Among such studies might be mentioned those of Hill,[1] Bruno Bloch,[2] Benham and Hopkins,[3] White,[4] and Pennington.[5]

PROCEDURE

A series of sixty-eight infants and children (thirty-three female and thirty-five male) with atopic dermatitis, who had not yet received any treatment, were studied. No attempt was made to separate those whose lesions resembled the superficial mycoses and others whose lesions did not. Scrapings of the lesions were taken from various parts of the body. These were (a) mounted in a 10 per cent sodium hydroxide solution and were examined microscopically; and (b) were cultured on Sabouraud's medium.

Intradermal tests were carried out with extracts of five of the more common fungi encountered in New York; namely, oidiomycin (1 to 100), trichophytin (1 to 30), *Aspergillus glaucus,* Rhizopus, and *Penicillium notatum.* The amount employed was 0.02 c.c. of extract (enough to produce the smallest wheal) intradermally and a first reading taken after fifteen minutes for evidence of an immediate reaction; a second reading was taken forty-eight hours later for a delayed, tuberculin-type reaction.

From the New York Skin and Cancer Unit, Department of Dermatology and Syphilology, The Post-Graduate Medical School, New York University-Bellevue Medical Center. Dr. Marion B. Sulzberger, Director.

RESULTS OF THE STUDY

Not one of the sixty-eight patients studied showed a positive reaction of either immediate wheal or delayed tuberculin-type to the extracts employed. (1) Microscopic examination of the scrapings taken from the lesions on various parts of the skin and treated with a 10 per cent sodium hydroxide solution failed to disclose any evidence of hyphae. (2) Cultures upon Sabouraud's medium, of scrapings of the lesions, failed to reveal the presence of any pathogenic fungi. The nonpathogenic fungi and bacteria found were penicillum species (one), *Aspergillus niger* (one), pink torula (two) bacteria (mostly saprophytic staphylococci) (eleven), other unidentified saprophytes (one), no growths fifty-two, with a total of sixty-eight.

CONCLUSION

The reported study confirms the generally held opinion that pathogenic fungi do not play a role in determining the clinical appearance of some lesions in atopic dermatitis. In the entire series of sixty-eight cases, not a single instance of a pathogenic dermatophyte was recovered. All skin tests for immediate wheal reaction and for forty-eight-hour tuberculin-type reaction with the extracts of fungi enumerated above were negative.

The author wishes to express his appreciation for the helpful suggestions and criticism rendered by Morris Leider, M.D., in charge of The Allergy Department at The New York Skin and Cancer Unit.

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FLUORESCEIN CIRCULATION TIME IN NORMAL AND PATHOLOGIC CONDITIONS IN INFANTS AND CHILDREN, INCLUDING VARIOUS TYPES OF CONGENITAL MALFORMATIONS OF THE HEART

BENJAMIN M. GASUL, M.D., JOHN J. MARINO, M.D.,
AND JOSEPH R. CHRISTIAN, M.D.
CHICAGO, ILL.

THE circulation time is the measured interval between the injection of a test substance into the circulatory system and its recognition by various methods. Substances with varying physical and physiologic end points have been used in the past to determine the circulation time. Many of these substances depend upon the subjective response of the patient. In infants and children it is often necessary and desirable to use a substance with which one can accurately determine the time without depending upon any subjective response. The fluorescein circulation time appears to satisfy this requirement. The simplicity of the procedure and the nontoxic properties of the test substance (sodium fluorescein) are further advantages.

The fluorescein circulation time was described by Lange and Boyd[1] in 1942 to determine the adequacy of the circulation in bowel obstructions and peripheral vascular diseases. They also stressed its diagnostic value in congestive heart failure, hypo- and hyperthyroidism, and suggested its clinical application in the diagnosis of congenital cardiovascular anomalies.

Sodium fluorescein is a resorcinolphthalein compound which is nontoxic when injected intravenously, and emits a brilliant green fluorescence when viewed under the long wave untraviolet lamp. It is rapidly excreted unchanged through the kidneys, giving a varying degree of brilliant green discoloration to the urine, depending upon its pH.[2] Relatively large amounts may be given in a single intravenous dose,[1] although in a few instances in our subjects it was noted that nausea and occasional vomiting may accompany doses of more than 4 c.c. regardless of weight of the patient.

PROCEDURE

The procedure was used on age groups varying from 15 days to 13 years. The calculated dose was approximately 0.7 c.c. per ten pounds of body weight of a solution containing dilution 5 per cent sodium fluorescein in 5 per cent sodium bicarbonate* as compared to Lange and Boyd's 0.7 c.c. per 10 kg. of body weight. The antecubital vein was selected as the site for injection and was entered with a 21-gauge needle. The room was darkened and the ultraviolet lamp was concentrated on the lips. The dye was injected as rapidly as possible, injection time averaging less than one second. The time interval between the beginning of the injection and the first appearance of a brilliant green fluorescence of the mucous membranes of the mouth was measured with a stop watch. The first appearance

From the Hektoen Institute for Medical Research, the Children's Division of the Cook County Hospital, and the Department of Pediatrics of the University of Illinois.
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*Manufactured commercially as "Fluorescite" by C. F. Kirk Co., New York, N. Y.

of this fluorescence was used as the end point, but a rapidly spreading fluorescence of the entire body resulted in all cases.

This report includes a series of 107 patients, fifty-seven of whom had demonstrable cardiac pathology and fifty who had no demonstrable cardiac disease. Of the former group, thirty-two conditions were congenital in origin and twenty-five were acquired.

RESULTS IN FIFTY NONCARDIAC CASES

In Table I it is shown that the arm-to-lip time varies with age. The circulation time from neonatal period through 2 years varied from 5 seconds to 8.5

TABLE I. CIRCULATION TIME IN NONCARDIAC CASES

PATIENT	AGE	WEIGHT (LB.)	DIAGNOSIS	AMOUNT (C.C.)	TIME (SEC.)
D. S.	4 mo.	11	Resolving pneumonia	1	7
J. M.	7 mo.	13	Resolving pneumonia	1	5
R. McC.	7 mo.	17	Resolving pneumonia	1	6
R. E.	9 mo.	17	Resolving pneumonia	1	6
C. H.	9 mo.	18	Resolving pneumonia	1.5	8.5
S. C.	12 mo.	20	Pulmonary tuberculosis	1.5	6.5
J. H.	12 mo.	23	Subglottic obstruction	1.5	5
J. J.	14 mo.	25	Normal	2	7.5
K. L.	19 mo.	28	Pneumonia	2.5	7
P. G.	20 mo.	29	Pneumonia	2	5
A. H.	22 mo.	33	Normal	2.5	7
S. McE.	2 yr.	27	Pulmonary tuberculosis	1.5	5
F. L.	2 yr.	21	Cerebrospastic	1.5	6
C. J.	2 yr.	27	Tuberculosis with effusion	2	9
K. D.	3 yr.	41	Melena	3	5
C. R.	3 yr.	22	Tuberculosis with effusion	1.5	6
D. J.	3 yr.	29	Pneumonia	2	7
N. H.	3 yr.	35	Cerebellar ataxia	2.5	8
D. J.	4 yr.	36	Epilepsy	2.5	6.5
A. K.	4 yr.	40	Pulmonary pneumonia	3	5.5
S. H.	5 yr.	40	Asthma	3	6
G. L.	5 yr.	41	Normal	3	7
G. J.	5 yr.	31	Laryngotracheitis	2.5	9
C. E.	5 yr.	39	Pulmonary tuberculosis	2.5	7.5
F. K.	5 yr.	40	Chronic bronchiectasis	3	9
W. L.	6 yr.	39	Normal	3	7.5
W. Y.	6 yr.	41	Pulmonary tuberculosis	2.5	9
G. K.	7 yr.	49	Chronic nephritis	3	6
R. C.	7 yr.	55	Tonsillitis	4	6.5
M. P.	7 yr.	50	Otitis media	4	7
R. S.	7 yr.	38	Tuberculosis	2.5	8.5
J. W.	7 yr.	50	Dermatitis medicamentosa	3.5	9.5
M. N.	8 yr.	58	Dermatomyositis	4	7.5
M. W.	8 yr.	50	Pneumonia	3.5	6.5
A. W.	8 yr.	57	Acute glomerular nephritis	4	7.5
B. L.	8 yr.	56	Histoplasmosis	4	8
F. C.	8 yr.	73	Erythema multiforme	5	10
G. F.	9 yr.	105	Nephritis	5	7
J. D.	9 yr.	51	Nonspecific adenitis	3.5	8.5
J. B.	10 yr.	80	Suspicious tuberculosis hilus	5	11
E. N.	10 yr.	96	Resolving pneumonia	5.5	12.5
C. C.	10 yr.	70	Epilepsy	5	13
A. P.	11 yr.	71	Diabetes	5	9
T. P.	11 yr.	60	Epilepsy	4	11
C. R.	11 yr.	59	Pulmonary tuberculosis	4	13
D. S.	12 yr.	86	Cervical adenitis	5	7
R. P.	12 yr.	70	Erythema multiforme	5	10.5
J. D.	12 yr.	79	Normal	4.5	10.5
D. J.	12 yr.	66	Tuberculosis with effusion	4.5	12
J. M.	13 yr.	75	Diabetes	5	7.5

seconds, with an average of 6.5 seconds. From 3 years through 13 years it varied from 5.0 seconds to 12.5 seconds, with an average of 8.5 seconds. The work of Witzburger and Cohen[3] on normal infants and children showed an average of 7 seconds in those from one to 24 months and an average of 11.5 seconds in the children from 3 to 13 years. In the older age group our series presented a more rapid circulation time than was found by Witzberger and Cohen. This variation may possibly be due to the larger amounts of sodium fluorescein used in our study.

Chronic or even acute pulmonary pathology, such as childhood tuberculosis, pneumonia, or asthmatic bronchitis produced no appreciable variation in the circulation time.

RESULTS IN FIFTY-SEVEN CARDIAC CASES

The circulation time of the cardiac cases as shown in Table II varies according to age just as in the noncardiacs. However, in congenital anomalies with a venous-arterial shunt there is a marked shortening of the circulation time, irrespective of age. In tetralogy of Fallot and transposition of the great vessels

TABLE II. CIRCULATION TIME IN CONGENITAL CARDIAC CASES

PATIENT	AGE	WEIGHT (LB.)	DIAGNOSIS	AMOUNT C.C.	TIME (SEC.)
P. W.	15 days	8	Interauricular septal defect	1	4.5
R. K.	3 mo.	12	Tetralogy of Fallot	1	2.5
S. C.	3 mo.	8	Tricuspid atresia, pulmonary stenosis, interauricular septal defect	1	3
M. M.	3 mo.	12	Interventricular septal defect	1	4
R. V.	5 mo.	12	Tetralogy of Fallot	1	4
B. O.	9 mo.	19	Tetralogy of Fallot	1	4
J. N.	9 mo.	18	Tetralogy of Fallot	1	5
S. A.	9 mo.	12	Possible pulmonary atresia	1	5
K. G.	14 mo.	20	Complete transposition of great vessels	1	2.5
B. F.	18 mo.	25	Common auriculoventricular valve	2	3
R. O'N.	18 mo.	17	Interauricular with mitral stenosis	1.5	7
R. O'N.	20 mo.	21	Interauricular septal defect	1.5	8.5
C. F.	21 mo.	37	Double aortic arch	2	5
M. J.	21 mo.	36	Interauricular defect	2.5	14
R. O'N.	22 mo.	21	Interauricular septal defect	1.5	9
R. McG.	2 yr.	25	Tetralogy of Fallot	1.5	3.5
R. H.	3 yr.	35	Tetralogy of Fallot	2.5	4
L. A.	4 yr.	40	Patent ductus	3	6.5
F. H.	5 yr.	41	Coarctation of aorta	3	7
P. M.	6 yr.	43	Patent ductus or interauricular septal defect	3	7
C. B.	6 yr.	50	Coarctation of aorta	3.5	6
M. W.	7 yr.	55	Complete transposition of great vessels	3.5	2.5
S. M.	7 yr.	55	Coarctation of aorta	4	7
D. C.	8 yr.	60	Tetralogy of Fallot	4	5
W. J.	9 yr.	53	Coarctation of aorta	4	9.5
L. G.	10 yr.	58	Coarctation of aorta	4	12
R. T.	11 yr.	95	Patent ductus or interauricular defect	6	9.5
J. S.	12 yr.	77	Lutembacher's syndrome	5	10
J. S.	12 yr.	77	Lutembacher's syndrome	5	11
G. F.	13 yr.	75	Tetralogy of Fallot	5	5
P. H.	13 yr.	110	Coarctation of aorta	5	9.5
P. H.	13 yr.	110	Coarctation of aorta	5	10.5

the time is shortened 3.0 to 4.4 seconds, with an average of 3.7 seconds. In other congenital anomalies, such as patent ductus Botalli, interauricular and interventricular septal defects, the circulation time was not altered in any appreciable amounts for the respective age groups.

The reason for the shortening in this former group, i.e., tetralogy of Fallot, etc., is that the blood as it enters the right side of the heart is shunted immediately into the systemic circulation via the dextraposed or transposed aortic vessel, thereby completely by-passing the pulmonary circuit. There is no change in the circulation time in isolated septal defects, due to the fact that the pressure is normally greater on the left side of the heart, thereby preventing any right-to-left blood flow. The amount of dye injected is small in comparison to the total blood volume and does not alter the already existing left-to-right shunt. The dye must, therefore, go through the pulmonary circuit before entering the systemic circulation; the reduction of the circulation time is definitely a diagnostic aid in determining the presence of a dextraposed or transposed aortic vessel.

TABLE III. CIRCULATION TIME IN ACQUIRED CARDIAC CASES

PATIENT	AGE (YR.)	WEIGHT (LB.)	DIAGNOSIS	AMOUNT C.C.	TIME (SEC.)
D. M.	2	28	Myocarditis	2	7
C. A.	4	40	Rheumatic heart disease	2.5	5
D. N.	4	40	Rheumatic heart disease	2.8	7
C. T.	4	38	Rheumatic heart disease	2	7
R. S.	5	45	Rheumatic heart disease	3.5	6.5
A. R.	5	50	Rheumatic heart disease with decompensation	3.5	12
A. G.	5	40	Rheumatic heart disease	2.5	8
V. B.	6	35	Rheumatic heart disease	2.5	9
C. N.	6	50	Rheumatic heart disease with decompensation	3.5	20
T. H.	7	48	Rheumatic heart disease	3	7.5
R. S.	7	48	Rheumatic fever	3	9
B. C.	8	58	Rheumatic fever	4	7
L. B.	8	55	Rheumatic heart disease	4	8
B. S.	9	51	Rheumatic heart disease	3	7
I. B.	9	50	Rheumatic heart disease	3.5	8.5
K. W.	9	65	Rheumatic heart disease	4.5	13.5
R. S.	10	65	Rheumatic heart disease	5	8.5
I. D.	10	60	Rheumatic heart disease	4	10
S. H.	10	60	Rheumatic heart disease	4	11
B. P.	10	60	Rheumatic heart disease with decompensation	4	21
H. B.	11	75	Rheumatic heart disease	5	11
W. F.	11	50	Rheumatic heart disease	4	13
O. W.	11	50	Rheumatic heart disease	4	13
J. D.	12	75	Rheumatic fever	5	10
E. J.	12	60	Rheumatic heart disease	4	11.5

There is no appreciable alteration of the normal circulation time in acute or convalescent rheumatic heart disease, as was shown in Table III. The average time for the acquired cardiac group was 9.2 seconds as compared to 8.5 seconds in the noncardiac group. However, in the presence of congestive heart failure there is marked prolongation of the circulation time.

SUMMARY AND CONCLUSIONS

1. The fluorescein circulation time, i.e., the time between the injection of fluorescein into the arm vein and the first appearance of the dye on the patient's lips, was measured in 107 patients.

2. In the normal noncardiac group, the average circulation time from the neonatal period through 2 years of age was 6.5 seconds. From three years to 13 years, the average was 8.5 seconds.

3. In tetralogy of Fallot where the aorta is dextraposed, or in complete transposition of the great vessels where the aorta comes off the right ventricle, as well as in tricuspid atresia with an interauricular defect, the fluorescein circulation time is markedly shortened to an average of 3.7 seconds.

4. The fluorescein circulation time is not appreciably altered in interauricular or interventricular septal defects or in patent ductus Botalli, coaretation of the aorta, or Lutembacher's syndrome.

5. The circulation time is not appreciably altered in acute or convalescent rheumatic heart disease except in congestive heart failure, where it is definitely prolonged, with an average of 17.7 seconds as compared to an average of 9.2 seconds in the compensated cases.

6. The fluorescein circulation time in infancy and childhood is a simple, nontoxic, inexpensive, objective procedure.

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AMELIA: REVIEW OF LITERATURE AND REPORT OF CASE

HERBERT H. POMERANCE, M.D., AND HYMAN SOIFER, M.D.
NEW YORK, N. Y.

CONGENITAL absence of all four extremities, known as amelia or amelus, is one of the more rare congenital anomalies. Few cases have been reported and little is known regarding the etiology of this tragic malformation. In view of the recent renewed interest in all congenital anomalies and their relationship to the virus diseases, we feel it timely to review the literature of this anomaly, add a case which has been under our observation, and discuss briefly the present concept as to causation.

In a review of the literature for a period of 100 years, we have been able to find authentic reports of only thirteen infants born with absence of all extremities. These cases[1-12] are tabulated in Table I. It can be seen that reports have been sporadic. The most recent case reported is that of Mooney[12] who discusses a family with multiple absences of extremities, and includes without comment a picture of one child born without either arms or legs. To this rather scattered series, we wish to add the following case.

TABLE I. AMELIA: REVIEW OF LITERATURE

AUTHOR	YEAR	NO. CASES
Vrolik[1]	1855	1
Hare[2]	1858	1
Slingenberg[3]	1908	1
Grassi[4]	1909	1
Price[5]	1928	1
Lukjanow[6]	1930	1
Lereboullet et al.[7]	1932	1
Levy[8]	1941	1
Killingsworth and Engledow[9]	1942	1
Otero[10]	1944	1
Hedenstedt[11]	1944	2
Mooney[12]	1946	1

REPORT OF CASE

A. J., a white female infant was admitted to Lincoln Hospital at the age of 12 days from the hospital in which she was born, because of absence of the arms and legs. She was the second child of American parents; the father was 28 years old, the mother 23 years old. The mother's first pregnancy resulted in a normal spontaneous delivery of a full-term female child in December, 1945. This child appeared normal at birth, and her development, both mental and physical, has been average. The last mensis prior to the second pregnancy began on April 29, 1947. There was no illness during any part of this pregnancy; the mother was vaccinated against smallpox, with primary take, on April 14, 1947. Diet during pregnancy appears to have been normal. She delivered a full-term infant on Feb. 7, 1948, after an uncomplicated labor of two hours' duration; birth weight of the child was 2,420 Gm.

From the Pediatric Service of Dr. Harry S. Altman at the Lincoln Hospital.

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The infant was transferred to this hospital for care on Feb. 19, 1948. Examination at that time revealed the general condition of the patient to be good; weight was 2,330 Gm. Search for congenital anomalies revealed none except for amelia (Fig. 1). Head circumference was 35.5 cm.; chest 32 cm.; abdomen 28 cm.; and total length 35.5 cm. Heart and lungs were normal.

Fig. 1.—Patient A. J., aged approximately 2 months. Note presence of small stump of right arm and toelike appendage representing left lower extremity.

Anus was patent. Nose, throat, and ears were normal. The left arm was completely absent, only a bud about 5 mm. in diameter being visible. The right arm was represented by a stump about 3 to 4 cm. long, which appeared to contain bone, and which could be moved by the patient. Shoulder girdles were present, and their mobility seemed normal. The right lower extremity was indicated only by a small, soft-tissue mass 1.5 cm. in diameter. The left lower

extremity was absent except for one toelike appendage with slight indentation of the distal end and two rudimentary nail beds. Hip girdles were present and appeared to have normal surrounding musculature; some attempt to move the rudimentary toe was made. X-ray examinations (Fig. 2) confirmed the presence of bone in the right upper and left lower extremity regions; the upper end of the right humerus was present, as were small bones representing one toe. Shoulder and pelvic girdles appeared roentgenographically normal for her age.

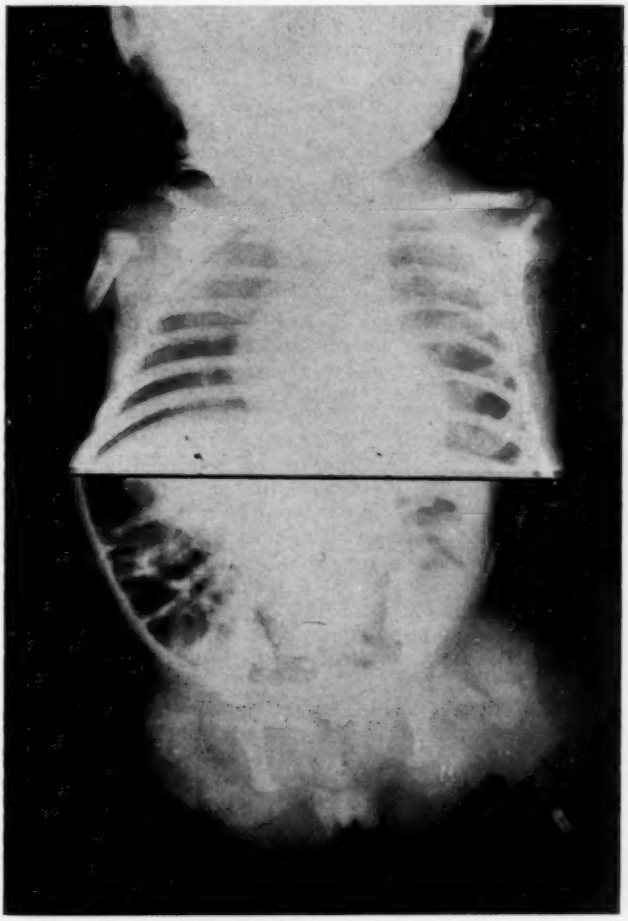

Fig. 2.—Patient A. J., reproduction of x-rays of upper (top) and lower (bottom) portions of body, showing absence of extremities except for stump of right humerus, and toelike appendage on left.

The course in the hospital was punctuated by frequent episodes of elevated temperature, for which no adequate explanation could be found, either clinically or by laboratory methods. However, her general condition was always good, and, on June 23, 1948, at the age of 4½ months, she was released

at the request of the parents, who desired to care for her at home. At this time her weight was 2,950 Gm.; she was quite active within her limitations, moving her head and the shoulder and pelvic girdles; her mental development appeared normal for her age.

The patient was readmitted on July 21, 1948 (aged 5 months), because of high fever of twelve hours' duration. On admission, her temperature was 108° F. per rectum; as before, she did not appear acutely ill and there were no positive findings to explain the elevation. Her weight was 3,100 Gm. With symptomatic therapy only, her temperature was reduced, became normal after two days, and then assumed an irregular course varying from 99° F. to 102° F. for the next two weeks. Complete laboratory work-up revealed no cause. At this point (aged 5½ months), she was again taken home by her parents. Her weight on discharge was 3,700 Gm.

Ten days after this second admission, the patient suffered another sudden rise in temperature to 106° F., and was taken to another hospital where she expired after twenty-four hours. No post-mortem examination was allowed, and it was the impression at the other institution that termination was caused by bronchopneumonia.

DISCUSSION

Arey[13] states that the buds which will form the extremities appear first during the fifth week of gestation (7 to 8 mm. fetus). These buds increase in size, the distal end of each flattens, and successive constrictions occur, so that the three parts of the extremity become apparent; grooves then indicate the position of the digits. These changes occur between the sixth and eighth weeks (approximately 11 to 25 mm. fetus). Differential growth subsequently results in the normal extremity. Meanwhile (Patten[14]), the primordium of the skeleton of the extremities appears as condensations of mesenchyme during the early part of the sixth week (12 mm. fetus); later during this week, some molding occurs, so that the positions of the main bones are suggested. The process of cartilage and bone formation then occurs.

Little actually is known in regard to causation of departures from this normal process of development of the extremities. It is hardly necessary to review here the numerous older theories, most of which are now discarded. Considerable attention has been given to the idea of developmental arrests, and this concept can explain the mechanism, if not the cause, of many anomalies.

The concept of developmental arrest depends upon the understanding that the rates of development of different parts of the embryo, and of the embryo as a whole, vary. Rapid progress alternates with relative inactivity. Within each developing part there is a critical short period of rapid multiplication, during which time this part differentiates and during which it dominates all other activity in the embryo. If anything interferes completely or in part with this process, the dominance is lost and is never regained; the next region then assumes its role and in turn becomes dominant. The result is an imperfect or even absent region, depending upon the time and degree of interference.

This concept of development is an interesting one in the light of which to consider the present case. We must postulate that during, probably, the sixth week of gestation, something interfered with the critical moment of differentiation of the extremities. This particular time-period is suggested by the evidence that limb budding apparently did start, and that some condensation of mesenchyme did occur, leading to an abortive laying down of

bone (right upper extremity and left lower extremity). It is reasonable to assume that the process need not be equally advanced in all extremities, and this would account for the varied stages of arrest.

Carrying the hypothesis one step further, it is possible that intercurrent disease in the pregnant woman, with its effect upon the embryo, could afford an opportunity for such developmental arrest, and the virus diseases recently incriminated in the production of anomalies fit into this category. We, therefore, inquired carefully into the history of the pregnancy which produced the child reported. We could find no evidence of rubella or of any other virus disease during early pregnancy. The fact that the mother was vaccinated was mentioned in the case report for the sake of completeness; the time relationship of the vaccination to the pregnancy rules it out as a factor.

With regard to the hyperthermia noted repeatedly in this infant, no definite explanation or mechanism can be offered. It is believed that a heat regulating center is present in the midbrain, which may prevent extreme rises in body temperature. Mechanically, control is a product of heat production versus heat loss by the body (Smith[15]). It was felt that poor control might have been a result of reduced skin surface for radiation of heat. However, there was also a lack of one of the major mechanisms for production of heat, to wit, contraction of the extremital muscles. Further elements in the heat regulation may be the sympathetic nervous system and the effect of adrenalin upon muscular activity. Which factor or factors may have been at fault here can merely be conjectured.

SUMMARY

Thirteen known cases of amelia, congenital absence of all extremities, are reviewed from the literature. An additional case is reported, with clinical and roentgenographic findings; an interesting feature of this case was the manifestation of unexplained, intermittent hyperthermia. A brief summary of the present-day concept of production of congenital anomalies in general, and amelia more specifically, is presented.

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SOLITARY RENAL ECTOPIA AND THE NEPHROTIC SYNDROME

RALPH H. KUNSTADTER, M.D. AND IRVING J. SHAPIRO, M.D.
CHICAGO, ILL.

ALTHOUGH renal ectopia is a congenital anomaly, one is struck by the infrequency with which this condition is mentioned in pediatric literature. The majority of reports are confined to urologic and surgical journals and texts and only Campbell contributes a comprehensive discussion on this subject for the pediatrician in his classic volumes of *Pediatric Urology*. The paucity of discussion on this subject in pediatric literature is particularly surprising in view of the fact that a great deal of what has been learned about congenital urinary tract anomalies has been acquired through the study of autopsy material on infants and children. Furthermore, symptoms and physical findings resulting in urologic studies occurred in infants and children in many of the case reports of ectopic kidney recorded in the literature. Also, congenital renal ectopia may offer a diagnostic problem such as occurred in our case before urologic studies were completed. Of further interest in our case is the nephrotic syndrome, and it was because of edema and albuminuria that the infant was hospitalized. To our knowledge, the nephrotic syndrome and solitary ectopic kidney have not appeared in the literature prior to this report.

CASE HISTORY

A 21-month-old male infant was admitted to Sarah Morris Hospital on March 30, 1948, for observation relative to generalized edema and albuminuria.

Five days before admission the mother noticed some puffiness of the eyelids, frequency of urination, and excessive thirst.

Previous History.—When he was 7 months of age his mother noticed frequent episodes of body shaking but no loss of consciousness; these episodes subsided spontaneously over a period of several months. At 9 months of age an eczematoid eruption of the extremities was observed. It was apparently due to egg sensitivity, and cleared after withdrawal of this food. The patient's 5½-year-old sister suffers from hay fever. At 11 months of age the patient was hospitalized for a severe streptococcus throat infection. At the onset his temperature was 105° F. and he had three convulsions in a period of six hours. He was treated with sulfadiazine and penicillin and made an uneventful recovery. One month later he developed a severe case of chicken pox with a maximum temperature of 104 to 105° F. for two days, but no convulsions occurred. At 14 months of age he experienced two severe attacks of bronchial asthma. At this time he was found to have an idiosyncrasy to barbiturates. He was not seen again until the onset of the present illness at 21 months of age.

Physical Examination.—Physical examination revealed a somewhat thin white male infant who did not appear ill. His weight was 26½ pounds and height 32½ inches. His temperature was 100° F. There was a moderate puffiness of the upper eyelids, the abdomen was large, dullness was present in both flanks, and a fluid wave was elicited. Pitting edema of the feet, ankles, and

From the Sarah Morris Hospital, for Children, Michael Reese Hospital, Chicago.

legs was present. A mild eczematoid eruption was present over both legs. The ears appeared normal. There was a clear mucoid discharge in both nostrils and the nasal mucosa appeared slightly boggy. The tonsils and pharynx appeared normal. The lungs were clear and the heart was normal. In spite of considerable abdominal distention and ascites, a mass was palpated in the abdomen. It was about the size of a medium-sized orange, apparently lobulated, firm, freely movable, and located low in the left lower quadrant about two inches to the left of the midline. No other masses were felt in the abdomen. Rectal examination revealed no impacted feces, and the mass could be palpated bimanually in the region of the sacrum between the finger inserted in the rectum and the hand on the anterior abdominal wall. Both testes were in the scrotum and no masses were palpated in the inguinal canals.

The initial impression was that of an intra-abdominal neoplasm, possibly renal in origin, omental cyst, a mass of mesenteric lymph nodes, probably malignant, or a hydronephrotic or cystic kidney. Further studies revealed the true nature of the pathology.

Laboratory Examination.—Urinalysis (Table I) revealed a grade 4 albuminuria, cylinduria, and an occasional red blood cell and white blood cell. Examination of the blood revealed no evidence of anemia. There was a slight increase in serum urea nitrogen, a marked hypoproteinemia, primarily due to reduction in albumin, and hypercholesterolemia (Table II). The blood pressure was 110/70. These findings are typical of the nephrotic syndrome and probably in this case are associated with a mild glomerulonephritis. In addition, however, a catheterized specimen of urine obtained during cystoscopic examination revealed on culture, *Escherichia coli* and *Aerobacter aerogenes*, indicating in all probability a secondary ascending infection resulting from obstruction of the urinary tract.

TABLE I. URINE

DATE	WEIGHT (LB.)	PH	SPECIFIC GRAVITY	ALBUMIN*	CASTS†	RBC†	WBC†
3/30/48	27	6.0	1.010	4	0	0	1-2
4/1	25½	7.0	1.008	4	0	3-4	2-3
4/2				4	occasional hyaline	3-4	3-4
4/5	25½	7.0	1.012	3	occasional hyaline	3-4	3-4
4/6	300 c.c. PLASMA			3			
4/12	27	6.5		4	0	3-4	many
	250 c.c. PLASMA						
4/13	26½	7.0	1.018	2	2	1-3	8-10
4/16	26¾	6.5	1.018	2	0	1-2	3-4
	250 c.c. PLASMA						
10/18	31	6.5	1.007	2	0	3-5	1-3
10/20		6.0	1.013	3	1-2 granular, occasional hyaline	1-2	4-5
10/28		250 c.c.	WHOLE BLOOD				
11/1		6.5	1.011	2	occasional granular	1-3	5-8
11/5		6.0	1.014	2	occasional hyaline	4-6	1-2
2/1/49	32	6.0	1.012	2	occasional hyaline	1-3	5-6

*Grade 1 to 4 denoting severity.
†Microscopic examination of centrifuged urine, high power field.

TABLE II. BLOOD CHEMISTRY

DATE	UREA NITROGEN (MG./ 100 ML.)	CHOLESTEROL (MG./ 100 ML.)	PER CENT EST.	TOTAL PROTEIN (GM./ 100 ML.)	ALBUMIN (GM./ 100 ML.)	GLOBULIN (GM./ 100 ML.)
3/30/48	28.0	260	66.0	4.0	2.7	1.3
4/5	23.5	416	65.0	5.4	3.4	2.0
4/12	32.0	503	62.0	4.7	2.3	2.4
4/16	38.0	584	52.0	5.3	2.7	2.6
10/18	37.0	358	67.5	5.9	2.5	3.4
10/30	34.5	---	---	---	---	---
11/5	43.5	---	---	6.3	2.5	3.8
2/1/49	29.0	306	70.0	6.9	3.4	3.5

An intravenous pyelogram revealed, at the end of five minutes, a moderate amount of opaque media overlying the left sacroiliac region and suggestive of an ectopic kidney (Fig. 1, *A*). There was no evidence of dye excretion on the right side. The amount of dye continued to accumulate until a large amount was present at the end of forty-five minutes (Fig. 1, *B* and *C*), at which time a large amount of dye was present in the urinary bladder. The bladder appeared normal except for the fact that external pressure was demonstrated on the upper and left borders, apparently due to the ectopic left kidney (Fig. 1, *C*).

Cystoscopic examination (I.J.S.) revealed that the bladder urine was grossly clear and the capacity and tolerance of the bladder was good.

The mucosa appeared normal throughout. The left ureteral orifice was normally placed and normal in appearance. It was easily catheterized with a No. 4 ureteral catheter for a distance of 15 cm. At the site of the normal right ureteral orifice there was a small dimple that could not be entered with either a catheter or a bougie. The urine from the left kidney was grossly clear and indigo-carmine injected intravenously appeared through the catheter in the left ureter only.

After retrograde instillation of 15 c.c. of Hippuran solution through the ureteral catheter, roentgenograms demonstrated the pelvis and calyces of a single ectopic kidney overlying the left sacroiliac region. There was dilatation of the pelvis and calyces and of the upper portion of the ureter, indicating hydronephrosis. Narrowing of the ureter was seen just inferior to the ureteropelvic junction, and this may represent a defect due to congenital stricture, or a congenital band or vessel (Fig. 2). However, the ectopic kidney was mobile so that it was felt possible that the ureteral defect was due to kinking.

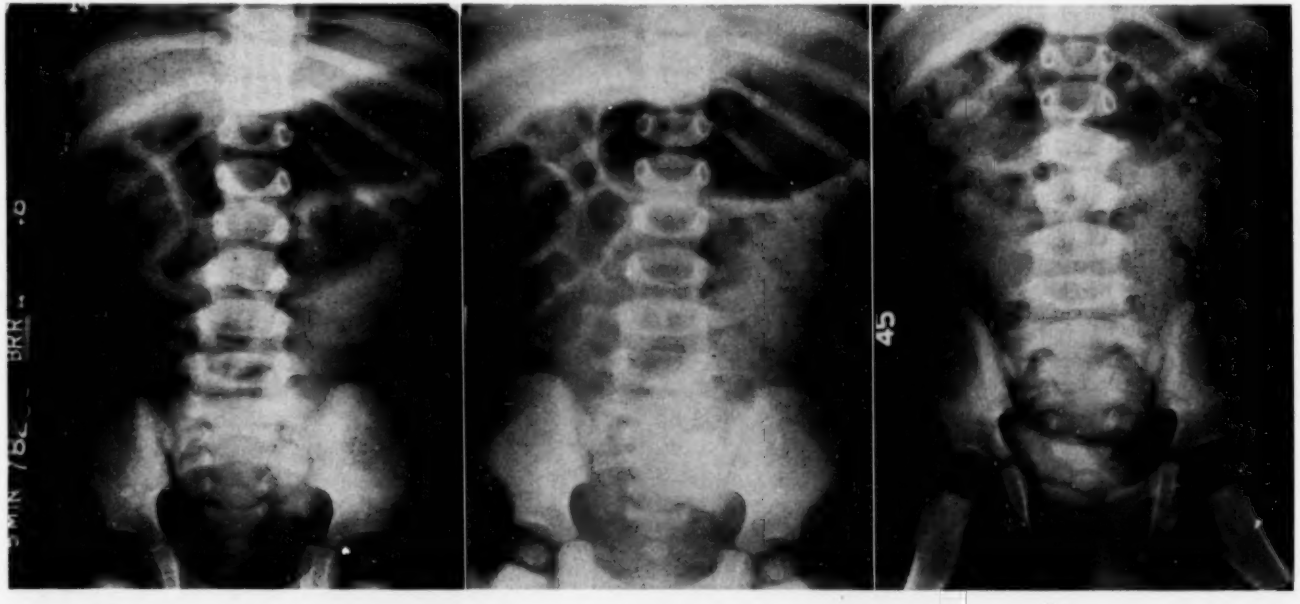
On the basis of the excretion urogram, cystoscopic examination, and retrograde pyelogram, a diagnosis of left ectopic kidney was established. The kidney, which lay over the left border of the sacrum at the pelvic brim, was enlarged and mobile. Palpation suggested that it was lobulated. Although there was some degree of hydronephrosis, function was fairly good, as evidenced by good excretion of dye and only slight retention of blood urea nitrogen.

Since no kidney or ureter was visualized on the right side, and on cystoscopic examination no right ureteral orifice could be demonstrated, it was our belief that there was no right kidney or ureter. However, without exploration congenital solitary kidney is difficult to differentiate from agenesis or nonfunctioning kidney due to aplasia or atrophy.

The patient was treated with a high protein, low sodium diet, transfusions of irradiated plasma,* and infusions of Amigen. After eighteen days he was discharged from the hospital clinically improved.

During the following six months he was readmitted to the hospital several times for treatment because of increased edema and albuminuria, which on two

*Plasma is irradiated in order to destroy hepatotoxic virus that may be present. (Samuel Deutsch Convalescent Serum Center.)



A. *B.* *C.*

Fig. 1.—*A*, Intravenous pyelogram reveals at the end of five minutes, a moderate amount of opaque media overlying the left sacroiliac region, suggestive of an ectopic kidney.

B, Accumulation of dye at the end of twenty minutes.

C, Accumulation of dye at the end of forty-five minutes, at which time a large amount of dye is present in the urinary bladder and the bladder appears normal except that evidence of external pressure is demonstrated on the upper and left borders, apparently due to the enlarged ectopic left kidney.

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occasions followed in the course of upper respiratory infections. The degree of albuminuria varied from 2 to 4 plus and the urinary sediment showed little change from the original findings.

On Oct. 18, 1948, approximately 6½ months after his initial admission, he was readmitted to the hospital for exploratory laparotomy. During the previous six weeks he was without visible edema and appeared in good health. However, the mass had increased somewhat in size, and appeared partially outlined against the left lower abdominal wall (Fig. 3). The increase in serum urea nitrogen, and consistently present red blood cells, white blood cells, and casts in the urinary sediment indicated that, in all probability, there had been further damage to the kidney (Tables I and II). A repeated intravenous pyelogram revealed little change over the findings noted on April 7, 1948, except possibly for a slight increase in the degree of hydronephrosis.

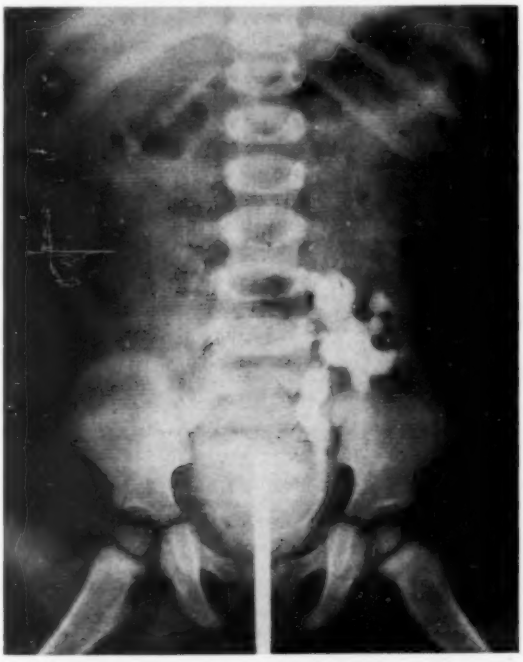

Fig. 2.—Retrograde pyelogram demonstrates the single left ectopic kidney overlying the left sacroiliac region. The calices, pelvis, and upper part of the ureter are dilated, indicating hydronephrosis. Narrowing of the ureter is present just inferior to the ureteropelvic junction, and this may represent a defect due to a congenital stricture, or a congenital band or vessel.

On Oct. 26, 1948, a transperitoneal exploration of the left kidney was done (I.J.S.) A large kidney protruding anteriorly toward the abdominal wall was found in the left pelvic region. The retroperitoneum covering the kidney was incised longitudinally and dissected free both laterally and medially. The kidney was retracted laterally and the pelvis was observed to be enlarged. The ureter was markedly dilated and tortuous, and at the ureteropelvic junction there was a pronounced angulation and narrowing. Palpation of this area gave the impression that the muscularis was absent and was replaced by fibrous tissue. At

the lower pole of the kidney a large vessel was palpated, apparently arising from the left external iliac artery. There was no encroachment upon the ureter in the region of this stricture. Adequate mobilization of the kidney was not possible and correction of the angulation of the ureter could not be accomplished. Exploration of the right side through the same incision confirmed the preoperative diagnosis of absent right kidney. The child made an uneventful recovery and was discharged from the hospital on Nov. 5, 1948, ten days postoperatively. At this time there was no edema. The urine contained 2 plus albumin, an occasional finely granular and hyaline cast, and occasional red and white blood cells. The urea nitrogen was 43.5 mg. per cent, the total serum protein 6.3 mg. per cent, the albumin fraction 2.5, and globulin 3.8 mg. per cent. He was reexamined on Feb. 1, 1949, three months postoperatively. There was no edema. The urine contained 2 plus albumin, and the findings on microscopic examination were unchanged. The urea nitrogen had fallen to 29 mg. per cent. The total serum protein was 6.9 mg. per cent, the albumin 3.4, and the globulin 3.5 mg. per cent.

Fig. 3.—The patient at 2 years, 3 months of age, five months after the initial hospitalization, and one month before exploratory operation. Edema and ascites have subsided. There is a visible prominence in the left lower abdomen, which is palpable as the ectopic kidney.

DISCUSSION

Congenital renal ectopia is not common but probably occurs more frequently than one is led to believe, because unless complications such as infection, stone or pain associated with urinary symptoms, or the finding of an abdominal mass occur, this anomaly may go unrecognized.

Campbell, in 1930, found twenty-seven instances of congenital renal ectopia in 14,400 autopsies in adults at Bellevue Hospital. Adding these to others reported in the literature, he found seventy-two cases in 47,477 collected autopsies, an incidence of one in approximately 600 individuals. In 12,080 autopsies in children, there were fifteen cases, an incidence of one in 800.[1] If one can visualize the number of cases which go unrecognized during life and realize the great number which never come to autopsy, one can easily conceive that the incidence must be considerably higher.

Solitary renal ectopia is apparently extremely rare. Stevens,[2] after a comprehensive review of the literature in 1937, estimated that solitary kidneys occurred once in every 700 to 1,610 cases, pelvic ectopia once in 2,150 to 3,000 cases, and solitary pelvic kidney once in 22,000 autopsies. He collected twenty-five reports of solitary pelvic kidney from the literature and added two cases of his own. Since this publication, eight more cases were found by Zuker,[3] who added a case of his own, making the total number of cases reported through 1946, thirty-six.

Other urologic anomalies frequently coexist with renal ectopia, particularly with the solitary variety. The anomalies may involve the upper or lower urinary tract or the genitalia, and it is not uncommon to find anomalies in other organs of the body.[4] Therefore, a careful examination of the entire body is indicated whenever renal ectopia is found.

Due to compensatory hypertrophy, the structural volume of the solitary kidney often approximates that of two normal organs and its functional output is increased correspondingly.[4] Hypertrophy and hydronephrotic dilatation were responsible for the large size of the kidney in our case.

Although congenital absence of one kidney is not incompatible with health, a single kidney is more likely to be the seat of disease than two normal kidneys. Pyelonephritis, hydronephrosis, and death by renal failure occur in rather a high percentage of these cases.[4] Fortune[5] reports 22.6 per cent kidney disease in 422 collected autopsy cases of solitary kidney as against the general autopsy average of 15 per cent. In Anders'[6] series of 170 cases of solitary kidney, seventy-nine kidneys were diseased.

The complication of the nephrotic syndrome is of extreme interest and added further difficulties in the management of our case. Although it has already been established that infection occurs more often in a solitary kidney than in twin kidneys, there is no evidence that points to congenital anomalies of the upper urinary tract as predisposing to glomerulonephritis or nephrosis. The nephrotic syndrome in our patient can best be explained as occurring in association with glomerulonephritis and secondary to the previous upper respiratory infections. The allergic phenomena and drug idiosyncrasies suffered by this patient may also be contributing factors in the etiology of the nephrotic syndrome.

In addition to the nephrotic syndrome and glomerulonephritis, our patient unquestionably has hydronephrosis and probably some degree of pyelonephritis secondary to the ureteropelvic obstruction. Because it was impossible to correct the underlying congenital ureteropelvic deformity, there is no reason to believe

that chemotherapy or antibiotic therapy will permanently eliminate the pathogenic organisms cultured from the urine. Consequently, the ultimate prognosis is poor, and in all probability, the hydronephrosis and pyelonephritis will progress.

CONCLUSIONS

Congenital ectopic kidney occurs at autopsy in approximately one to 600 or 800 individuals. Considering the number of cases of congenital ectopic kidney that are unrecognized, the actual incidence is probably a great deal higher than the autopsy incidence. Solitary ectopic kidney is extremely rare, but in view of the fact that disease is more prone to occur in such a kidney during early life, its recognition is more likely to occur during infancy or childhood.

The presence of an abdominal mass in an infant or child, particularly in the lower quadrants, should suggest the possibility of an ectopic kidney. Erroneous diagnosis of neoplasm, mesenteric cyst, mesenteric adenitis, appendicitis, ileocecal tumor, tuberculosis, etc., can be avoided by thorough urologic study in all cases of abdominal mass with or without urinary symptoms, and/or a pathologic urine. A simple clinical test that may aid in the establishment of diagnosis of a kidney mass is that of palpation or massage, which frequently will produce transient albuminuria in a patient whose urine was previously clear.[4]

Although operative intervention proved to be a failure in our case, and apparently will be in most instances of solitary ectopic kidney, there is always the possibility that a coexisting anomaly may be corrected. Therefore, when anomalies of the ureter and hydronephrosis exist, we believe that exploration is justified. If correction is not possible, destruction of the kidney and renal failure ultimately will occur.

SUMMARY

A case of solitary pelvic ectopic kidney observed in a 21-month-old infant is reported. The infant was seen initially because of the nephrotic syndrome, and the ectopic kidney was found on subsequent examinations. On the basis of laboratory findings, it was believed that the nephrotic syndrome was associated with glomerulonephritis. Surgical exploration confirmed the clinical findings. Hydronephrosis secondary to congenital angulation of the ureter and ureteropelvic obstruction was present. Due to anomalous blood supply, mobilization of the kidney and correction of the ureteral deformity could not be accomplished.

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Case Reports

ANOMALOUS ORIGINS OF THE RIGHT COMMON CAROTID AND RIGHT AND LEFT SUBCLAVIAN ARTERIES ASSOCIATED WITH EISENMENGER'S COMPLEX

HAROLD W. BISCHOFF, M.D., FERNANDO R. LEYVA, M.D., AND
E. CLARENCE RICE, M.D.
WASHINGTON, D. C.

THIS case of anomalous origins of the subelavian arteries and the right common carotid artery in association with Eisenmenger's complex has various interesting characteristics both from the anatomical and embryologic points of view.

CASE REPORT

This 5-month-old female infant was well until two days before her hospital entry, when she developed a respiratory infection which seemed to be localized mostly in the chest. At the onset of her illness there were fever and cough. The day before hospital entry she began to vomit and continued to do so all that day and the following day. There was no history of cyanosis.

The past history revealed that the child had been treated in The Children's Hospital Dispensary for an infection of the upper respiratory passages two months before. There had been impetigo and thrush at 3 months of age. The child had been considered to be a Mongolian idiot since birth.

Prenatal history revealed that the mother had vomited throughout the entire pregnancy. The delivery and neonatal period were normal.

The maternal grandparents were deaf mutes and there also was a history of diabetes in the maternal antecedents.

Physical examination at the time of hospital entry revealed a well-nourished and well-developed white female child with Mongoloid facies. There was a wide neck which was continuous with the occiput. The pharynx was injected. The chest was symmetrical. Rough breath sounds and rhonchi were heard and the respirations were labored. The heart rate was normal, the heart was not enlarged to percussion, and no murmurs were heard. The fifth digits of the hands were rather short and curved toward the ring fingers.

A chest film taken on the day of entry showed an increased radio-opacity over the upper three-fourths of the left chest. There was also a dense hilar shadow on the right which was thought to represent an enlarged lymph node.

The child did poorly during her hospital stay. The temperature spiked to 105° F. on the second and fourth hospital days. In spite of penicillin and sulfadiazine therapy the child died.

Necropsy Findings.—The body was that of a well-developed and well-nourished white female infant of stated age measuring 60 cm. in length and weighing 4.88 kg. The eyes were slightly slanted and there were bilateral epicanthal folds. Even in death the muscles were extremely hypotonic. There was very little rigor mortis even at four hours. The thumbs inserted at right angles to the hands; however, there were no simian lines. There was no Mongolian spot at the base of the spine.

Upon entering the thoracic cavity, the heart was seen to be extremely large. The great veins entered in normal fashion. The aorta appeared to emerge

From the Medical Service of Edward Lewis, M.D., and the Department of Pathology, The Children's Hospital, Washington.

more to the right than normal. There was no innominate artery; instead the right common carotid and subclavian arteries arose from the aorta, side-by-side, at the same level. The left common carotid artery arose from the aorta immediately above the latter. The ductus arteriosus arose from the pulmonary artery, proceeded cephalad anterior and to the left of the left main bronchus and entered the aorta at the arch. The left subclavian artery arose from the middle of the ductus arteriosus. The latter structure was 7 mm. in length. That portion of the ductus on the pulmonary artery side was anatomically closed while the lumen on the aorta side was as large as the subclavian artery which arose from it.

Upon opening the heart it was noted that the musculature of the right ventricular wall was one-half again as thick as that of the left ventricle. The valve measurements were as follows: tricuspid 6.5 cm., pulmonary 3.7 cm., mitral 5.0 cm., aortic 3.0 cm. There was a large interventricular septal defect measuring 2.7 by 1.2 cm. which occurred in the pars membranacea of the septum. The aorta was dextroposed and the right wall was immediately above the septal defect. The valves contained their normal numbers of leaflets and the coronary arteries arose normally.

The posterior aspects of both lungs were red-purple in color and quite hard to the touch. The middle portions of both lungs were dark red in color and firm. The anterior portions of both lungs were light pink in color and crepitant. On section the posterior portions showed marked infiltration with blood, the middle portions were very dark pink in color, and fluid could be expressed from the cut surfaces. The anterior sections appeared normal.

The liver was enlarged, light in color, and appeared edematous.

The brain was somewhat smaller than the cranial vault and showed evidence of cerebral agenesis.

The remainder of the organs were within normal limits.

Microscopic Examination.—In the lungs, the walls of the alveoli were thickened and the capillaries were engorged. Some serous fluid and a few cellular elements were present in the lumina of a number of the alveoli. Mononuclear cells and a rare polymorphonuclear leucocyte were present in the interstitial tissue.

The muscle fibers of the heart muscle were separated, showing very distinctly the branching of the myocardial fibers. There were some rather large nuclei present.

Histologically the remainder of the organs showed a generalized red cell engorgement.

Discussion.—Origin of the left subclavian artery from the ductus arteriosus is described by Taussig[1] in association with absence of the aortic arch. The origin of the latter anomaly is ascribed to the overmigration of the heart in its caudad movement. In the case described, the left subclavian artery arose from the center of the ductus arteriosus; however, the aortic arch was present.

Since both the right subclavian and the right common carotid arteries arose side-by-side from the aorta and rotated through 90 degrees from their usual relations and also since the left subclavian artery arose from the ductus arteriosus, it might be inferred that, in its embryological development the heart migrated farther caudad than normal enough to rotate the arteries on the right through the 90 degrees and sufficiently to cause the left subclavian artery to arise from the ductus arteriosus, but not sufficiently to cause the descending aorta to become continuous with the pulmonary artery, with consequent obliteration of the aortic arch.

The external appearance of the heart and the anomalous origins of the arteries are shown by the drawing in Fig. 1. The over-all blood circulation is

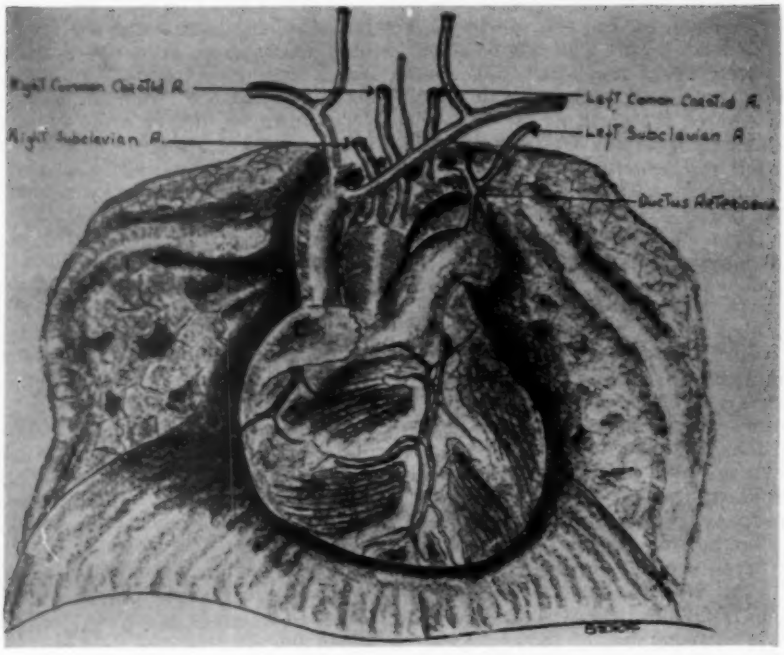
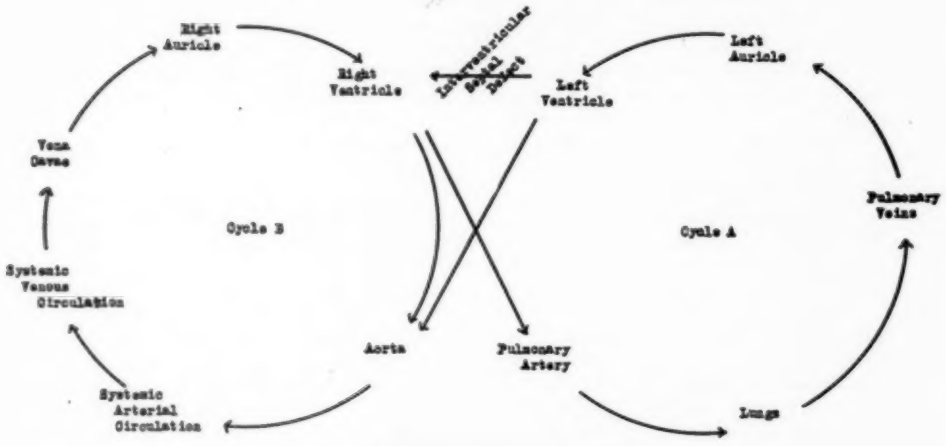


Fig. 1.—Drawing showing external appearance of heart and anomalous vessels.



ANOMALOUS HEMODYNAMOGRAM

EISENMENGER'S COMPLEX (ASSOCIATED WITH ANOMALOUS ORIGINS OF RIGHT COMMON CAROTID AND SUBCLAVIAN AND LEFT SUBCLAVIAN ANEURISM).

Fig. 2.

shown by the hemodynamogram[2] in Fig. 2. The dextroposition of the aorta is shown by the paired arrows going to the aorta from the right and left ventricles and naturally means that blood from both ventricles reaches the aorta.

Considering the heart under discussion, where the aorta did not actually override the septal defect, there would be less tendency for unoxygenated blood from the right ventricle to escape into the aorta. One might consider, however, that a Venturi effect existed which would draw unoxygenated blood into the aorta as the fast-moving stream of blood passed the orifice in the ventricular septum.

Blood will pass from an area of higher pressure to an area where the pressure is lower, hence the arrow depicting the interventricular shunt is drawn as passing from Cycle A to Cycle B, i.e., from the left ventricle to the right. This would follow the normal picture where the pressure within the left ventricle is higher than the pressure within the right ventricle. However, a fact which should not be neglected in the case under discussion is that pressure exerted upon a fluid is transmitted equally in all directions. Considering the fact that the right ventricular wall was one-half again as thick as the left, having potentially greater muscular power available, the pressure within the right ventricle should have been higher than that in the left ventricle, and unoxygenated blood should have passed from Cycle B to Cycle A.

Since cyanosis did not dominate the clinical picture, we might infer that the amount of unoxygenated blood reaching the systemic circulation by way of the interventricular septal defect and by direct injection into the aorta must have been at a minimum. Undoubtedly, as data are accumulated on intracardiac pressure studies the directions of blood flow will be elucidated.

SUMMARY

1. A case of anomalous origins of the right common carotid and right and left subclavian arteries associated with Eisenmenger's complex in a Mongolian idiot, is presented.

2. Some embryological considerations are reviewed in an attempt to explain the probable source of the anomalous origins of these vessels.

3. Theoretical considerations of the direction of blood flow are discussed in an attempt to correlate the clinical picture with the anatomical findings.

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DEEP VEIN THROMBOSIS IN A NEWBORN INFANT

MAURICE J. KELLER, M.D.
SALEM, MASS.

DEEP venous thrombosis in the extremities during infancy and childhood is an extremely rare occurrence. Search of both American and foreign literature on the subject fails to reveal a single instance of peripheral venous thrombosis in this age group unaccompanied by serious systemic infection or marasmus consequent on a debilitating disease. In a thorough review of pulmonary embolism and infarction in infancy and childhood, Zuschlag[1] studied thirty-eight cases from the Mayo Clinic, only four of which were associated with thrombus formation in the major channels of the extremities. All of these involved the femoral vein and were associated with severe infection either in close proximity to the affected veins or at some distant location. Zuschlag[2] further gathered sixty-four cases of pulmonary infarction in the younger age groups from the literature. Among these, only two were associated with thromboses in peripheral veins, one each in the femoral and crural veins. The former occurred in a 4½-year-old child in the course of severe measles,[3] and the latter in a 9-year-old child who also had pericarditis, myocarditis, and thrombosis of the longitudinal sinus.[4]

The following case is reported because of its uniqueness in the absence of any demonstrable local or systemic infection, and because an unusual diagnostic procedure in this age period was employed successfully as corroborative evidence of the clinical diagnosis.

CASE REPORT

L. P., a 9-day-old white male infant of Jewish parentage, was admitted to the Mount Sinai Hospital Pediatric Service on June 3, 1947, because of cyanosis and swelling of the right lower extremity of twenty-four hours' duration. The infant was the product of an uncomplicated full-term pregnancy and delivery, and throughout his first eight days he appeared normal in all respects. A ritual circumcision was performed on the eighth day of life at the maternity hospital. During the procedure the patient's grandfather, who was described as an unusually large and powerful man, held the infant about the upper thighs with thumbs pressed in the region of the inguinal folds. At one point during the operation the grandfather was reprimanded because of the unusual pressure which his thumbs appeared to be exerting in both inguinal regions of the baby. Another less enthusiastic member of the group held the infant during the remainder of the ceremony. There was no unusual bleeding, nor were any other difficulties encountered in the actual operative procedure.

Nine hours after the circumcision and twenty-four hours prior to admission the mother noted the infant's extremities to be cool and slightly bluish. This did not alarm her at the time, but during the succeeding twelve hours the right lower extremity became progressively colder, more deeply cyanotic, and definite swelling was noted. During this period the left leg regained its normal color and again became warm. There appeared to be no impairment of the baby's general condition, he took his breast feedings well, moved all his extremities actively, appeared in no distress, and remained afebrile.

From the Department of Pediatrics, Mount Sinai Hospital, New York, N. Y.

Physical examination on admission revealed a well-developed and nourished lusty male infant who did not appear ill. The rectal temperature was 99° F., pulse 120 per minute, and respirations 30 per minute. The patient was very active and moved all his extremities through their full range. With the exception of the penis, right lower extremity, and skin over the lower abdomen, the examination was negative. The glans penis was mildly ulcerated with minimal fresh bleeding from its surface. There was no evidence of infection, and the penile shaft was of normal color and warmth. The right lower extremity was cyanotic and cool from Poupart's ligament anteriorly, and posteriorly from the major gluteal fold. The entire leg was edematous but no pitting could be demonstrated. The circumference of the midthigh was 3 cm. greater than a similar point on the opposite extremity, and the right calf circumference exceeded that of the left by 2 cm. No femoral pulsation could be felt on the right, but with pressure over any point on the leg immediate blanching occurred with rather slow restoration of the previous cyanotic color as the pressure was released. The skin over the right lower abdomen was definitely dusky, and in this area there were several prominent veins in which the blood flow was cephalad. There were, in addition, multiple fine telangiectases in the same region.

Laboratory.—Hemoglobin was 14.5 Gm. per 100 c.c.; white blood cells were 20,000 with 65 per cent mature polymorphonuclear leucocytes, 3 per cent nonsegmented leucocytes, 25 per cent lymphocytes, 6 per cent monocytes, and 1 per cent eosinophiles. Platelets numbered 200,000 per cubic millimeter, and there were less than 0.5 per cent reticulocytes. The bleeding time was 2½ minutes, clotting time 4½ minutes with good clot retraction at the end of one hour. The urine was normal. A roentgenogram of the abdomen and lower extremities revealed only soft tissue swelling of the right lower extremity.

Course.—The patient's general condition remained excellent throughout his seventeen-day hospital stay, there was no fever at any time, feedings were taken well, and weight gain was satisfactory.

The findings on admission suggested venous obstruction involving the major vessels of the right lower extremity, possibly extending into the right iliac vein, in addition to arterial spasm in this member and possibly some element of lymphatic stasis. The evidence appeared to favor phlebothrombosis rather than thrombophlebitis and an operative procedure with ligation of the affected vessel was considered. However, in view of the uncertainty regarding the nature and extent of the pathology, a period of observation was decided upon, and at the same time heparinization of the infant was started. Intravenous heparin in a dosage of 1 mg. was administered at hourly intervals for twenty-four hours, with prolongation of capillary clotting time from an initial four minutes to eighteen minutes. At this point, twenty-four hours after hospitalization, the right lower extremity was definitely warmer than on admission, was less edematous and cyanotic, and a good femoral pulse could be made out on this side. No abnormalities had appeared in the left lower extremity. The telangiectasia over the right lower abdomen had increased, dilated venules now were seen around the umbilicus and also above Poupart's ligament just to the left of the midline. From this point intramuscular heparin was to be administered at eight-hour intervals, but through an oversight which was not detected for twenty-four hours it was omitted. Nevertheless, the capillary clotting time during the period of omission of heparin continued prolonged, varying between twelve and fifteen minutes. Forty-eight hours after admission to the hospital improvement in the leg had become so marked that further heparinization was deemed unnecessary. By the third day the clotting time had returned to values

obtained on admission. The course in the following ten days was one of progressive and almost complete disappearance of all previously described abnormalities of the circulation in the part. A few dilated venules over the right upper anterior thigh remained, and these, too, had disappeared by the thirteenth hospital day. When complete clinical clearing was evident, a venogram, using two injections of 5 c.c. of a 35 per cent Diodrast solution for posteroanterior and lateral films, was performed via a cannula inserted into the right external saphenous vein. The patient was discharged well on the eighteenth day after onset of symptoms. He was seen four months after discharge, at which time he appeared entirely well. Both lower extremities were equal in length and in circumference at several points, and skin temperatures were the same in both extremities. There was not a trace of a superficial venous channel over the abdomen or legs. No abnormalities of the extremities had presented at any time following discharge.

Fig. 1.—Phlebogram, right leg, lateral view. Note absence of deep system, striking number of tortuous collaterals, and deformity of femoral bulb (arrow).

COMMENT

Interpretation of phlebograms, even by those very experienced in this technique, is often difficult because of frequent variations in the normal and because of pooling of the injected dye in normally patent veins, depending on speed of injection and actual positioning of the extremity when the exposures are made. Since no mention of phlebography in the age group of this patient could be found in the literature, the problem of interpretation without either normal

or abnormal films for comparison would appear all the more difficult. Despite this, the venogram in this instance shows characteristics of obstruction repeatedly emphasized and agreed upon in authoritative works on the subject.[5-7] Thus, the accompanying illustration shows complete failure of filling of the deep venous system of the leg from a point just below the origin of the common femoral vein, a filling defect at the junction of femoral and saphenous veins (marked by arrow), and finally a striking number of tortuous venous collaterals. These abnormalities in the venogram, together with the clinical picture and course of this infant, leave little doubt as to the primary diagnosis of venous thrombosis.

Although the etiology of venous thrombosis is still not entirely clear, and though there continues to exist considerable disagreement among authorities on the subject, nevertheless certain fundamental conditions necessary to thrombosis are generally admitted.[8-15] These are: first, changes in the blood itself, such as increased coagulability as occurs in thrombocythemia or in severe hemoconcentration; second, changes in the blood flow with slowing and formation of eddies; and third, changes in the vessel wall itself, whether as the result of mechanical or chemical trauma or of infection. The patient described presented at least two of these three major factors, namely, slowing of the venous flow in the lower extremities and unquestionable local injury, both as a consequence of unusually severe pressure exerted in the region where the vessels are quite superficial.

The clinical picture seen on admission to the hospital indicated a much more widespread phenomenon than could be accounted for solely by the presence of an obstructive process in the major venous channels of the leg. Thus, there was probably a large element of contiguous arterial spasm as indicated by the loss of femoral pulsation on the side of the presumed thrombus. In addition, the extremity was definitely cooler than the opposite side, it was cyanotic, and blanching on very slight pressure could be demonstrated. The fact that an area blanched by pressure could restore its circulation rather quickly would indicate incomplete arterial closure by the spasm. The nonpitting edema of the leg suggested some lymph stasis as well as a more diffuse tissue disturbance resulting from impaired arterial and venous circulation with concomitant lowering of temperature of the part.

The condition of very transient mild cyanosis and diminished temperature of the left lower extremity was probably associated with a vasospastic phenomenon related to the pressure exerted in the left inguinal region at the time of the circumcision. This would seem to be analogous to the situation not infrequently arising following femoral puncture in which there is some difficulty in transfixing the vein, with possible excessive trauma to this or to its fellow artery. Cyanosis and lowering of temperature of the leg may then occur, only to subside completely within a few hours of onset. The mechanism of widespread arterial and probable venous spasm which occurred in the right leg in this case might well be compared to the situation in adults in whom lumbar sympathetic block may result in prompt relief of many of the circulatory changes in an extremity which is the site of a venous thrombosis.[16, 17] Reflex phenomena mediated through the network of sympathetic plexuses in the adventitia of veins and of arteries in close proximity to veins may thus result in an area of circulatory embarrassment far from the original site of injury. Lumbar sympathetic block was not felt to be indicated in this instance in view of the rapid improvement after a short period of observation, and because of the truly remarkable and apparently adequate collateral circulation which developed with such great rapidity. Extension of the

thrombus with possible serious embolization was feared, and so heparinization was begun, although not carried beyond a twenty-four-hour period. In retrospect, lumbar sympathetic block as soon as the patient was seen might have been a logical procedure, since much of the circulation of the leg would have been restored rapidly, thereby eliminating at least the factors of continued stasis and deficient nutrition which conceivably might have led to extension of the thrombus. Long-term sequelae of deep venous thrombosis, although frequently seen among adults, could not reasonably be expected to occur in the age group of this patient.

SUMMARY

A case of major venous thrombosis in the right lower extremity of a newborn infant is described, with commentary on probable etiology and associated pathologic changes. The diagnosis was confirmed by phlebography.

The author is indebted to Dr. Samuel Karelitz and Dr. Ralph Moloshok of the Mt. Sinai Hospital Pediatric Service for their advice and interest in the study of this case.

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INTUSSUSCEPTION IN A NEWBORN INFANT

MARGARET PROUTY, M.D., HAROLD W. BRUSKEWITZ, M.D.,
AND GEORGE P. SCHWEI, M.D.
MADISON, WIS.

CASE reports of intussusception occurring at birth, or in the first few days after delivery, are rare in the literature. We wish to present such a case, of interest not only from the standpoint of the immaturity of the infant, but also because of the absence of some of the most important criteria on which to base a diagnosis.

The infant was brought to us on the third day of life with the chief complaint of bleeding from the rectum. The father, who brought the patient to us from some distance, was unable to give any history, and we did not obtain one for twenty-four hours.

This female infant was delivered on the evening of Oct. 20, 1948, by an osteopath in a private hospital. Delivery was without incident, and routine care was given. The following day the baby was put to breast and given a commercial formula. The stools were of normal meconium. That evening a slight blood staining was noted in the meconium; it was noted again at each diaper change throughout the night. By 5:00 A.M. on October 22, the infant was still nursing well and passing blood-stained meconium, but there now occurred an emesis of the feeding, followed by a brown-colored vomitus. The abdomen was not rigid, and no masses could be palpated. Rectal examination was negative. A high enema was ordered. Vitamin K was started, and amino acid was given subcutaneously when fluids were refused by mouth. The attending osteopath examined the abdomen several times throughout the day, and each time the physical findings were essentially negative. At no time was there evidence of pain or discomfort. Slight bleeding from the rectum continued, however, and a local pediatrician was called who suggested that in the absence of obstructive symptoms, the Rh factor was probably at fault.

On entry, the infant was alert, and appeared to be in no distress. Jaundice was evident, and the temperature was 103.4° F. rectally. The abdomen was soft, nontender, and no masses could be palpated. Bowel sounds appeared normal. The cord was healing satisfactorily. There was fresh blood on the diaper, and clots and bright red blood were seen to ooze from the rectum occasionally. The admitting officer believed that he had felt a mass in the rectum, but it had immediately moved upward from his finger and could not be felt again either in the rectum or abdomen.

Vitamin K was injected in the buttocks. Feedings were withheld pending further examination. The Rh of the father and mother were reported as positive. The infant's blood count was as follows: red blood cells, 5,950,000; white blood cells, 12,500; 16 Gm. hemoglobin; bleeding time, 1:53; and coagulation time, 2:15. Surgical and proctologic consultation was requested.

An infant proctoscope was used. The rectal canal admitted the instrument with ease, and it was advanced to an 8 cm. level without difficulty. No abnormalities were noted. At approximately 10 cm. the entire lumen of the canal was occluded by a bluish, congested, shiny mass. No lumen was seen in the mass, and during the course of observation this mass moved upward and disappeared from view. It could not be definitely determined if this mass was the end of an intussuscepted bowel or a rectal polyp on a long pedicle. We were inclined to believe that the latter was correct.

From the Department of Pediatrics, Jackson Clinic, Madison, Wis.

The infant still showed no distress. Two ounces of formula were now taken by mouth, and somewhat later an additional ¾ ounce was consumed.

Finding it difficult to believe that we were dealing with an intussusception in the absence of clinical signs, we held the infant under observation until morning.

She was then found to be weaker, somewhat dehydrated, and had a slightly bluish discoloration surrounding the navel. The abdomen for the first time showed slight resistance, but still no masses were palpable. The diaper contained about 2 to 3 c.c. of dark blood, and there had been no stool passage. Projectile emesis of a rather large amount of greenish stained vomitus occurred.

Surgery was now believed to be imperative, and the child was fortified with subcutaneous fluids and a small whole blood transfusion. X-ray studies of the colon had been unsatisfactory, as the barium had been expelled almost as soon as injected. However, a flat plate of the abdomen showed considerable air under both leaves of the diaphragm. There was definite dilatation of some of the loops of the small bowel.

The peritoneal cavity was exposed through a lower left rectus incision and revealed several ounces of cloudy fluid speckled with barium. The small bowel was moderately distended. An elongated mass was palpable from the rectosigmoid to the splenic flexure. A 2.5 cm. by 1 cm. perforation was seen at the sigmoidal flexure. Telescopic colon was seen through the perforation, and its distal portion extended to the rectosigmoid juncture. This was brought up through the perforation and proved to be the cecum, appendix, and a portion of the ileum. The complete intussusception was then reduced. The cecum, the entire ascending colon, and 4 cm. of the ileum was gangrenous. The right half of the colon and 6 cm. of ileum were resected, and an end-to-side anastomosis of the ileum and transverse colon was done. Because of the unusually large perforation and the presence of several 1 cm. by 1 cm. necrotic areas at the lower one-third of the descending colon, it was necessary to resect 8 cm. of the left colon and perform an end-to-end anastomosis. A mixture of penicillin and sulfathiazole powder was instilled in the peritoneal cavity, and the wound was closed in layers. At the conclusion of the operation the respirations became labored and finally ceased. The pulse was still perceptible, and despite positive pressure, oxygen administration, artificial respirations, and intravenous injections of a stimulant, the patient expired.

The pathologic report does not throw much new light upon the situation, except that there was massive hemorrhage into the wall of the specimen around the region of the ileocecal valve, and no lumen could be identified grossly there.

COMMENT

Reports of intussusception in the neonatal period are not completely new in the literature, as there have been thirteen reported as having occurred in the first six days of life. Of particular interest to us are those which have occurred in the first two days postdelivery. Lewis[4] lists the first case of jejunal intussusception occurring in a one-day-old infant. Perrin[5] published a monograph based on 400 cases, the youngest patient being one day old. Jeffrey[2] reported the third case in a one-day-old infant. Gelston[1] cites the case of the baby who passed clots by rectum on the evening of the second day, vomited on the third day, and died of intussusception on the fifth day without surgery. To make our record complete Tweedy[6] mentions the newborn infant who had hemorrhage from the bowel on the second day and died on the third day of an intussuscepted bowel.

It is our feeling that our infant developed this condition during the first day of the postdelivery period. Ladd[3] states that the blood usually appears at the fourth to twelfth hour after intussusception occurs.

In this case we were dealing with an infant with massive gangrene, perforation, and peritonitis, and yet who showed no sign of cramping, distention, rigidity, or distress, which usually attend such a condition. We wish to point out that such diagnostic criteria may be absent in the newborn infant.

SUMMARY

The sixth case of intussusception occurring in the one- to two-day-old infant is reported. It is of especial interest because the usual diagnostic criteria were absent even though gangrene, perforation, and peritonitis were present.

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Clinical Conference

CONFERENCE AT THE CHILDREN'S HOSPITAL OF SAN FRANCISCO, JAN. 4, 1949

PEDIATRIC DEPARTMENT

Case 1. Xanthomatosis

H. E. THELANDER.—The case presented today is of interest because at the age of 6 months when first seen on Jan. 19, 1947, the patient presented a picture of unmistakable skin xanthomatosis combined with marked hepatosplenomegaly and a blood picture not unlike a leucemia. The history revealed that at the age of 3 months a small red bump resembling a mosquito bite first appeared on the forehead. It began to enlarge and turn yellow, finally reaching the stationary size of a small pea. Further small masses developed on the top of the head about two months later. These evolved similarly but in general were smaller in size. There were no other presenting symptoms.

There was no history of abnormality in birth, development, or feeding; there were no previous diseases other than three mild upper respiratory infections; and there was no similar condition in the family.

On examination the temperature, pulse, and respirations were normal. The skin showed typical xanthomata over the scalp. There were numerous lesions, varying from a pinhead up to a split pea in size. There were small areas of brownish discoloration over the skin of the forehead. The skin of the remainder of the body was free of lesions. There was a moderate pallor. The head was normal in size, with fontanels not unduly large. The eyes were rather widely spaced and prominent. Throat, chest, heart, and lungs were negative. The spleen was enlarged, reaching midway to the iliac crest. The liver extended 3 fingerbreadths below the right costal margin. There was no tenderness. Genitalia, extremities, and neurological examination were negative. The lymph nodes were moderately enlarged, discrete, and nontender.

Complete blood count revealed: hemoglobin, 6.2 Gm.; red blood cells, 3.2 million; white blood cells, 45,700. The differential count was polymorphonuclears, 42; nonfilamented, 31.5; eosinophiles, 2.5; basophiles, 5; lymphocytes, 47; monocytes, 3.5; unclassified, 3; blast cells, 1.5. Examination of urine revealed only an occasional white blood cell. Sedimentation rate 3 mm. per hour. Blood chemistry was: blood total cholesterol 101.6 mg. per cent; serum phosphorus, 5.1 mg. per cent; alkaline phosphatase, 2.3 Bodansky units; cephalin flocculation, negative. Kolmer and Kahn negative. Sternal marrow aspiration showed promyelocytes, 0.8 per cent; and of myelocytes, neutrophiles, 6.4 per cent, eosinophiles 5.0 per cent, polymorphonuclears nonfilamented 24.0 per cent and filamented 1.8 per cent. Plasmacytes were 0.4, promonocytes 2.8, monocytes 18.4, pro-erythroblasts 0.8, erythroblasts 7.2, megakaryocytes 0.4, and histiocytes 1.8.

X-ray studies reported the skull and chest negative; the long bones showed "Non-reactive periosteal calcification along the shafts of the large long bones."

Biopsy of the scalp lesion was reported as a "granulomatous lesion with lipoid holding cells."

The patient was placed on a low cholesterol diet. Supplementary iron and brewers' yeast was given.

On April 11, 1947, the patient was rehospitalized because of an acute upper respiratory infection accompanied by fever to 104° F., cough, and cervical adenitis. Throat culture revealed Beta hemolytic streptococcus. The patient became afebrile in four days with penicillin and supportive therapy. A restudy of the general systemic disease at this time revealed hemoglobin 9.3 Gm., red blood cells 3.98 million, white blood cells 36,350, polymorphonuclears 39, nonfilamented 29, lymphocytes 52, unclassified 11. Skull x-rays revealed no significant changes. Skeletal x-rays revealed "cortical hyperostosis of the large long bones." Biopsy report on an axillary lymph node and scalp lesion was "reticulosis with lipoid storage." The lipoid was not identified but studies showed that it was not neutral fat.

On May 5, 1947, the patient entered the hospital for a blood transfusion. In the interval from May, 1947, to September, 1947, a total x-ray radiation dose of 400 R. was delivered over the posterior and anterior trunk and 300 R. to the scalp. New cutaneous lesions began to appear on the neck and thorax; however, the general condition seemed improved. The liver and spleen decreased slightly in size. From November, 1947, to May, 1948, there were frequent upper respiratory infections and fever. There had been several episodes of rather severe epistaxis. A moderate anemia had gradually developed. On March 3, 1948, hemoglobin was 54; red blood cells, 2.78 million; white blood cells, 15,400; polymorphonuclears 47; eosinophiles, 3; basophiles, 0; lymphocytes, 44; monocytes, 6. Although development was retarded, the baby was now able to walk and say a few words. The mental age appeared to be about one year. Physical examination revealed additional significant findings. There was moderate protrusion of the eyes with slight bossing of the frontal bones (head circumference 20⅛ inches). The cervical lymph nodes were somewhat larger than previously. The liver was enlarged to 6 cm. below the right costal margin, the spleen was enlarged to 6 cm. below the left costal margin. There was a spadelike appearance to the hands and marked bilateral calcaneovalgus of the feet. Complete blood count after transfusion revealed a hemoglobin of 10.5 Gm.; red blood cells 3.77 million; white blood cells, 23,250; polymorphonuclears, 48; filamented 34; nonfilamented, 14; eosinophiles, 2; basophiles, 1; lymphocytes, 30; plasmacytes 10, metamyelocytes, 7; myelocytes, 2. X-ray examination showed that since previous examination on April 22, 1947 "the right parietal bone had developed faint striations, increased density, and apparent mottled areas of decalcification." There was "possible elevation of the orbital roof but there was no evidence of bone destruction."

The fourth hospitalization occurred Aug. 31, 1948. About two months before this entry anemia became more marked. Further small transfusions were given and frequent febrile episodes were treated with penicillin. One week before entry further x-ray therapy was directed to the liver and spleen. Physical examination revealed a marked pallor, prominence of the eyes, and skin lesions present on the back and buttocks. The abdomen was markedly distended

with the liver and spleen each palpated 12 cm. below the midcostal margins. Both were firm and nontender. The fingers appeared noticeably shortened.

Complete blood count showed: hemoglobin 10.7 Gm.; red blood cells, 3.42 million; white blood cells, 17,350; polymorphonuclear, 18. Lymphocytes were 81; monocytes, 2; platelets, 160,000; packed cell volume, 37 per cent; sedimentation rate, 18. Blood cholesterol total was 69.5 mg. per cent, free, 50 mg. per cent.

Treatment consisted of transfusions, penicillin, and other supportive measures. However, the baby remained febrile and became weaker throughout hospitalization. For the last three weeks there was a marked susceptibility to cutaneous infections. A marked spontaneous drop in white blood cells from 17,000 to 3,000 occurred ten days before death, and platelets dropped to 60,000. A week before death 7 doses of aminopterin 0.5 mg. was administered.

A few days before death a progressive anal cellulitis appeared. The patient died on Sept. 23, 1948, at 26 months of age.

J. T. CRANE.—This infant, upon examination, was quite emaciated; the head appeared to be somewhat prominent, that is, the cranial vault seemed prominent as contrasted to the facial bones. The eyes were slightly protruding, though it was not definitely established that exophthalmos was present. There was xanthomatous lesions varying from a few millimeters to 12 cm. in diameter over the scalp, neck, and thorax. In addition, there were small vesicular lesions of an inflammatory nature over the body. The abdomen was greatly distended due to the enlarged liver and spleen.

Of the internal organs, the liver and the spleen were the most remarkable. The liver weighed 1,400 grams, which is about the normal size for an adult. It was finely mottled; it had rounded edges and was quite firm in consistency. The spleen was likewise enlarged, weighing 225 grams. It, too, was firm and showed, upon close inspection, accentuation of the trabeculae and miliary foci.

The lungs were striking in so far that they contained in the subpleural regions yellow nodules, often flat but occasionally spherical.

Examination of the heart, kidneys, and gastrointestinal tracts showed yellowish nodules in the subepicardial and endocardial regions of the heart, in the subpelvic regions of the kidneys, and in the submucosal areas of the gastrointestinal tract.

The lymph nodes were of two types. Those about the pancreas were large, up to 3 cm. in diameter, somewhat red, and fleshy. Other nodes, those of the cervical region and about the lower abdominal aorta, were somewhat yellow in color and firm in consistency.

The brain was of normal size and showed grossly what was thought to be areas of increased firmness throughout the cortex. However, this finding was not substantiated by microscopic examination.

The skull showed definite punched-out areas about ¼ to ½ cm. in diameter in both the parietal and frontal bones. There were also yellowish depositions in the medullary portions of the base of the frontal and the sphenoid bones.

The periorbital fat appeared slightly increased and somewhat edematous, which probably accounted for the slight prominence of the eyes. There were no bony defects to account for the exophthalmos.

Microscopic examination of the liver revealed the periportal connective tissue increased in amount. The increased cellularity was due to accumulations of histiocytes, a certain amount of fibroblasts with collagen deposition, and a few inflammatory cells, some of which were eosinophiles. There were a few free megakaryocytes in the sinusoids of the liver. The special stains showed no appreciable amount of lipid deposition in the liver.

The spleen showed an increase in cellularity both intra- and intersinusoidal. The intersinusoidal cells consisted chiefly of histiocytes. These cells showed no evidence of lipid storage. The intersinusoidal cells consisted of histiocytes, megakaryocytes, occasional myelocytes, and normoblasts. Throughout the miliary areas that we saw grossly were accumulations of histiocytes.

Sections of the lymph nodes showing a yellow color about the periphery revealed that many of the cells with clear cytoplasm were histiocytes; through the cortex of the gland was found moderate dilatation of the sinusoids. These sinusoids were filled with blood and blood-forming cells. Megakaryocytes were common throughout.

Sections of the lung through the yellow plaques found these to be composed of diffuse sheets of closely packed histiocytes, some of which contained clear cytoplasm. Examination of such lesions under polarized light definitely established the fact that there was cholesterol. However, there was also a moderate amount of lipids present, as well as we could ascertain by our staining technique. So the lipid characteristic of this disease was probably a mixed one. It was not a pure cholesterol deposition.

All the bone marrow that was examined showed involvement. There was no normal bone marrow present. This involvement was quite characteristic. In areas of considerable cellularity, the cells again were histiocytes. Occasionally they contained considerable amounts of lipid material. Other areas of bone marrow showed a fibrosis, so evidently these histiocytes were not only differentiating toward a lipid storage type of cell or actually a macrophage, but they also apparently had the potentiality to become fibroblasts.

In some areas there was complete replacement of bone marrow by reticuloendothelial cells.

J. T. LANMAN.—There are two aspects to this case which are of more than passing interest. The first of these relates to the consistent finding of abnormal cells in the circulating blood during the two years that this case was followed and detailed hematologic reports were made. Although these cells are variously described by different observers, there seems little doubt but that the essential character of the differential remained unchanged throughout the course of the illness. On the other hand, the total white count showed a persistent fall from the striking leucocytosis on the first examination to the leucopenia observed on the last admission. To my limited knowledge this type of blood change has not been reported in the literature in association with xanthomatosis, although the finding of certain other bizarre abnormal cells in the peripheral blood is, of course, not unusual, and in Niemann-Pick disease it occurs to such an extent that the large fragilocytic cells which are released into the circulating blood are said to block the pulmonary capillaries, where they are filtered out, presumably on the basis of size. It was our impression at the laboratory that this picture was

consistent with leucemia and that the trial of aminopterin might afford some benefit, although on the whole our experience with this drug has not been encouraging. It was fortunate in this case that a blood count was done immediately before the beginning of aminopterin therapy for, in this instance, although the results of this blood count were not known until after therapy was instituted, it marked the beginning of a definite and striking fall in the white count which, because of its onset definitely before the beginning of aminopterin therapy, must in all likelihood be ascribed to the spontaneous course of the disease. Because of the profound leucopenia, aminopterin was quickly discontinued and not restarted until two days before death, at which time the leucopenia had somewhat abated. There has been considerable discussion as to whether these cells in the blood might represent circulating histiocytes. At our present state of knowledge this appears to me to be a somewhat fruitless argument, but at the laboratory where our smears are studied by the supravital technique it was our impression that the cells were of the lymphocytic series although somewhat bizarre in appearance. There would appear to be no particular reason why, in a disease of this nature which is characterized by extensive reticuloendothelial hyperplasia, occasional cells of an unusual nature should find their way into the circulating blood.

A second feature of considerable interest in this case are the transitional characteristics between the various types of xanthomatosis which it represents. The evolution of thinking in regard to this group of diseases during the past forty years is of extreme interest. Hand was the first to describe a pathologic report of the case, representing what is now known as Hand-Schüller-Christian's disease. In his original report it was his impression that the most likely diagnosis was tuberculosis, although certain atypical features of the case led him to suspect his own diagnosis. Some years later Schüller described the x-ray changes which are characteristic of the disease and shortly thereafter Christian recognized the symptom triad from lesions in the bone, exophthalmos, and diabetes insipidus. It is now well recognized that these findings and symptoms are dependent purely on the chance location of the xanthomatous infiltration and that in any given case any one or perhaps all of this triad may be missing.

At about the same time a disease entity now known as the Letterer-Siwe's disease was first being described, pathologically by Letterer and later clinically by Siwe. The clinical entity described was one of hepatosplenomegaly and generalized glandular enlargement with a hemorrhagic diathesis, a progressive and invariably fatal course, and on pathologic examination an extensive, generalized proliferation of the reticuloendothelial tissues. In contrast to certain other forms of xanthomatosis it was thought that this disease was both nonhereditary and nonfamilial. Although on superficial examination it might appear that there was little in common between these two diseases, it was pointed out by Waldron in 1940 that the differences which did exist were no more extensive than might be encountered in any single disease entity with its varying manifestations. It was his impression that so-called Letterer-Siwe's disease presented a more fulminating disease which, in its more chronic form, was clinically recognized as the Schüller-Christian syndrome. In support of his contention he cited a few cases which appeared to be transitional between the two forms of the

disease. It was also in 1940 that Lichtenstein and Jaffe first described what they thought to be a new disease entity and for which they proposed the name eosinophilic granuloma of bone. These were usually solitary lesions in which the x-ray picture was confused with certain other entities as, for example, giant cell tumor of bone which on pathologic examination showed a bizarre picture in which the infiltration with the eosinophiles was the most striking characteristic, but in addition to the eosinophilia a highly pleomorphic picture was presented. Because many of the conditions with which this picture was confused were highly malignant, the benign prognosis of the eosinophilic granuloma was the more striking. It was rapidly pointed out, however, by Farber and others, that this so-called "new disease entity" was in actual fact not a new one but it had been recognized previously and, in the opinion of Farber, represented but one stage of the osseous lesions of the Schüller-Christian syndrome. The numerous transitional cases between typically eosinophilic granuloma of the bone and the Schüller-Christian syndrome, and the frequent pathologic impossibility of distinguishing the two conditions rapidly led to a degree of agreement that the diseases were at least very closely related. However, it is my impression that it is still open to question whether or not in a given case of Schüller-Christian's disease with bone lesions there is anything like an orderly progression of the pathologic picture which at some stage or other will represent the picture of eosinophilic granuloma of bone; or, conversely, whether eosinophilic granuloma of bone will heal by resolution or through the stages of connective tissue scarring which are more characteristic of the Schüller-Christian syndrome. In the main, however, there has been a great simplification of thinking with regard to various disease entities which fall under the heading of xanthomatosis, and indeed it is not clear that xanthomatosis is a proper name for this group of diseases at all, inasmuch as the current thinking about the group seems to indicate that the fat storage is purely facilitative. The case which we are discussing fairly clearly represents the transitional stage between Letterer-Siwe's disease and typical Schüller-Christian's although it is striking that the first manifestation of the disease was the xanthomatous infiltration of the skin of the scalp. It is also striking that this infiltration occurred at a very early age so that it is certainly clear that extreme chronicity is not necessary to the appearance of xanthomatous lesions in Schüller-Christian's disease. It may also indicate that more than a simple time factor is involved in determining whether a specific case will or will not show fatty infiltration.

DR. PEARL SMITH.—There are a number of confusing things about this case. The lesions were so brilliantly pigmented that I fully expected to find a rather heavy deposit of cholesterol. I think there is some question as to whether the cells in the blood really should be called monocytes. Where there is as much proliferation of reticuloendothelial cells as you can see in this case (and I thought definitely some of them seemed to be rounding up and separating) they might easily get in the blood stream.

DR. CRANE.—My understanding was that the lesions were not yellow at first but like a mosquito bite.

DR. THELANDER.—The lesions varied from time to time. Sometimes they were distended, shiny, and intensely yellow, and at other times they were flattened out and looked almost like crystals of yellow material under the skin; as they faded they would assume a reddish hue. Likewise the new ones when they first appeared often looked like red hives that would gradually become more yellow.

DR. E. B. SHAW.—At about the same time as this child was seen we had several newborn or young infants who had a number of xanthomatous lesions on the scalp and body. It does not take long for a lesion to develop from a size you do not notice to one that is quite obvious. There was little difference in these completely benign lesions from those early present in this case.

DR. THELANDER.—The liver and spleen were sent to the university laboratory for chemical studies but this report is not yet available. The case presented was a most interesting and instructive case to follow and study. The patient has shown some manifestation of practically every type of case grouped under the heading of xanthomatosis from reticuloendotheliosis at one end of the spectrum through Letterer-Siwe, Hand-Schüller-Christian to monocytic leucemia on the other. The two years showed little evidence of progression from one phase to another and it is likely that such a concept of xanthomatosis is erroneous.

Case 2. Pertussis in an Immunized Infant

DR. EDWARD B. SHAW.—We now consider a problem which is becoming a rarity in private practice: a case of pertussis in a 22-month-old infant who had been immunized previously. This brings up the problem of immunization, its effectiveness, the age at which immunization is preferable, and finally, the treatment of the acute symptoms. Dr. Randolph, the interne, will present this case.

DR. RANDOLPH.—E. D., a 22-month-old white female infant, was admitted to the communicable disease ward Jan. 19, 1949, with a complaint of paroxysmal cough for one month. This child had been well previously, and the cough was initiated with a slight coryza, with a fever of 38.4° C. on only one occasion. For a period of three weeks before hospital entry the cough had become progressively worse, a characteristic whoop developed, and there was attendant vomiting.

This infant was immunized during the period of July 12 to Aug. 15, 1947, aged 3 to 4 months, by a physician in a Southeastern state, using three injections of a saline suspension of killed *Hemophilus pertussis* totaling 100 billion organisms.

There was a convincing history of exposure to whooping cough in an urban housing development.

Physical examination at entry showed nothing beyond the evidences of continued whooping cough in an infant. The child was exhausted, pale, and had obviously lost considerable weight. The paroxysms of coughing were unmistakably those of pertussis, and were accompanied by a loud whoop and considerable cyanosis. There were no evidences of complication apart from the exhaustion and malnutrition.

Blood count showed hemoglobin 13.0 Gm.; red blood cells 4.7 million; white blood cells 14,700; polymorphonuclears 59 per cent (8 nonfilamented), lymphocytes 34 per cent, eosinophiles 1 per cent. The sedimentation rate was normal, the urine was negative. Throat culture contained a few gram-negative rods which were not identified as *H. pertussis;* a conventional cough plate was also negative for *H. pertussis.*

The child had received on the second and third day before admission 20,000 units of Antipertussis Endotoxin—a rabbit serum product provided by Wyeth. In the hospital the infant was treated with streptomycin aerosol, 50 mg. every two and one-half hours. Paroxysms increased in frequency and severity over the first four hospital days. On the second hospital day a few scattered rhonchi and musical râles were heard throughout the chest; at this time the chest film showed no evidence of consolidation. On the third hospital day one-half cubic centimeter of pertussis vaccine (20 billion organisms) was given intramuscularly. By the fifth hospital day the paroxysms definitely decreased. On the fifth day she was discharged home greatly improved, and the improvement has continued at home.

Although bacterial confirmation was lacking, there seemed to be no doubt of the diagnosis. Evaluation of therapy was difficult. The anti-endotoxin administered before entry seemed not to be of benefit, although this may have contributed to the rapid improvement in the hospital. Streptomycin aerosol was not spectacularly effective. The recall injection of pertussis vaccine was succeeded by rapid improvement, although this may have been coincidental. Final improvement may have depended upon nursing care, one or another of the therapeutic agents, or simply the effect of time.

DR. WILLIAM J. KERR.—In addition to attempted specific therapy this child received various antispasmodic drugs but the effect of these was equally hard to evaluate. Oxygen was used only as a means of administering the streptomycin aerosol.

DR. SHAW.—We have two visitors who are interested in the question of immunization and therapy brought up by this case. Dr. Deamer, would you like to open this discussion?

DR. W. C. DEAMER.—The point which Dr. Kerr suggested I comment on particularly was that of the efficacy of early immunization to pertussis. I am glad to have the opportunity to review the evidence for and against immunizing infants with pertussis vaccine before the customary six-month age period. I have personally been loath to do this, as I had the impression that there was fairly good evidence that immune mechanisms were not as efficient in the very young animal as they were later on. This impression has been strengthened by my review of the evidence.

To begin with, it may be well to point out that all antigens are not equally antigenic and that were we discussing diphtheria or tetanus toxoid as an antigen, the score might be different. These, by comparison with pertussis vaccine, are considerably better antigens. Some of the early failures of pertussis immunization relate to its poor antigenic qualities. The presently recommended high

doses of pertussis vaccine also attest this fact. Since we are dealing with one handicap in this respect, the existence of another possible handicap becomes of especial concern, lest the double handicap compound the failures of immunization which we will encounter.

The evidence that the immune mechanism in the very young animal is not comparable to that of the older animal is varied. Freund and Baumgartner demonstrated in several species of animals and with several different bacterial and other antigens a difference in favor of the older animal in quantitative antibody response. There is evidence in the German literature that newborn infants respond less well to typhoid vaccine than do adults. French authors have shown that older children respond to diphtheria toxoid better than younger children. The development of natural antibodies such as isoagglutinins also points in the same direction. They are not usually present under one month nor do they reach adult levels until 2 years of age. There are a good many additional articles indicating a similar improvement in antibody production with age. These include a wide variety of antigens and several species of animals including the human being.

On yet another somewhat theoretical ground, one might expect better antibody response in the older child than is found in the younger child. Although the young infant usually has a high serum globulin level, the gamma fraction decreases progressively after birth. We know that many immune antibodies are carried in this gamma fraction.

While the above comments do not necessarily constitute a complete indictment against early immunization with pertussis vaccine, they certainly form a challenging argument against its complete acceptance. The evidence would seem to be against very young infants giving a very good response. Here we are likely to fall into a battle of words, as the question naturally arises as to how good the response must be, and this cannot be answered catagorically. It may be well to point out how extremely variable the response to pertussis vaccine and other antigens is. In a study of tetanus toxoid several years ago we obtained over one hundredfold variation in antitoxin formation in a group of 150 infants given the same antigen in the same manner. If the group had been larger the range of variation would undoubtedly have been larger also. This variability of antibody response has been demonstrated right down the line and includes pertussis vaccine. The question then is not how many in a group respond exceptionally well, but how large the group of poor responders is, for it is among them that the failures will occur. The recent article of di Sant' Agnese on the immunization of newborn infants indicates to me that the group of poor responders to pertussis vaccine among the newborn infants is too large. Forty-six per cent were without a "protective" titer of pertussis serum agglutinins one month after the last of three injections of a triple vaccine. In a comparable group of older infants this author had previously found only fifteen per cent without a protective titer. The evidence against the relative response of the younger infant is clear even if we disagree as to what constitutes a protective titer.

Thank you, Dr. Shaw. I shall be interested in hearing your opinion and that of Dr. Miller on this interesting question.

DR. SHAW.—Apart from the effect of age of immunization there is also the question of variation in antigenicity of vaccine. Dr. Bower told me last week in Los Angeles that he had observed a series of failures in pertussis immunization which he had traced to a single vaccine. He stated that this particular preparation proved to be a very poor antigen, was a decidedly rough strain and not a Phase 1 organism. It was his opinion that such failures would not infrequently, and perhaps unavoidably, be encountered. Dr. Miller, do you want to carry on?

DR. J. J. MILLER.—This youngster provides an excellent example of the failure to protect with a dose of 100 billion saline-suspended *H. pertussis*. Four reasons why this child might not have been protected are: she might have been too young; she might have been a congenitally poor reactor; the lot of vaccine employed might not have been potent, for there has been no certain way to standardize the potency of vaccine; and the fact that the vaccine used was suspended in saline, not precipitated with an adsorbent. The evidence that infants under 6 months of age can be protected with whooping cough vaccine rests first and foremost on the field study of Wallace Sako and his collaborators in the United States Public Health Service in New Orleans. They injected a total of 40 billion alum-precipitated *H. pertussis* in three divided doses at monthly intervals, beginning in the second month of life. It was possible to follow almost 2,000 injected infants and a like number of controls for a period of one to two years. During this time the secondary attack rate following familial exposure was over 80 per cent in the control group whereas it was less than 20 per cent in the inoculated group. This statistically significant evidence of protection was in contrast to earlier reports on the protective efficacy of vaccine at such an early age. Incidentally, these workers were able to demonstrate that clinical protection was associated in these infants with the carriage of serum agglutinins in high titer (that is, 1-320 or more), a finding previously reported from our clinic.

The remaining evidence in favor of early immunization is supportive but indirect. There has been no other field study reported. The supporting evidence consists of a report by Dr. Halper of Texas, in which was employed the same product at the same age as Sako. The immune response was gauged by serum agglutinin estimations and the development of antibody in the skin. To this may be added the report of di Sant'Agnese and some work that we have done at Stanford during the past four years.

In our experience 40 billion alum-precipitated *H. pertussis* will induce and maintain for one year levels of serum agglutinin consonant with immunity in 60 per cent of infants. This does not mean that only 60 per cent of the infants were protected. The presence of agglutinins in low titer following vaccine and even the absence of agglutinins does not imply susceptibility. Sako found that in vaccinated infants with titers below the critical level of 1-320, the secondary attack rate varied inversely with the titer and reached a maximum of 33 per cent in those infants carrying no agglutinins. Thus it is fair to estimate, I believe, that the precipitated vaccine we employed protected 60 per cent of the infants plus one-half of the remainder, or a total of 80 per cent.

There is, I think, adequate evidence to say that the ability to immunize varies directly with age. It is a question of what percentage of individuals you can

immunize at a certain age and whether you can immunize enough to make it practicable. There will always be some individuals whom you cannot protect regardless of age. It is our belief, based on the report of Sako and supportive evidence that I have mentioned, that it is practicable and advisable to attempt immunization beginning at 4 to 8 weeks of age, providing a precipitated or adsorbed product is used. There is considerable evidence that such adsorbed antigens are more effective immunizing agents than saline-suspended vaccine.

We have seen children who received saline-suspended vaccine under 6 months of age who contracted pertussis, just like your patient. We have not yet seen infants who had received precipitated vaccine develop pertussis, but of course we will see some sooner or later.

DR. PATRICIA CLARK.—Dr. Miller, I should like to ask your opinion regarding the effectiveness of a recall dose of vaccine. This child unfortunately received no booster dose. I saw her a short time before the onset and recommended a booster dose, but this was deferred because the child had a slight upper respiratory infection. Can you compare the protection in those who have had only immunization in infancy with those who have had one or more booster injections during the next few years?

DR. MILLER.—That depends on the three factors: type of vaccine used, whether it was precipitated or adsorbed; the total dose; and the efficacy of the immunity factor of that individual. Using saline-suspended vaccine in a total dose of 80 billion, reports from widely different sources have indicated that secondary attack rates following familial exposure vary from about 10 per cent to 30 per cent. I think one can conservatively say that in an older child these injections will protect two out of three children exposed in the home and four out of five children exposed in the school or elsewhere.

DR. BAUMANN.—Dr. Miller, how would you feel about using a combined vaccine which is not, as I gather, completely precipitated but only partly so, such as Tri-immunal with a lesser concentration?

DR. MILLER.—We use Tri-immunal, alum-precipitated occasionally. I think it is good. However, the total dose of *H. pertussis* in the recommended total volume of 1½ c.c. is only 30 billion. I believe that is inadequate. I think you ought to give at least 40 billion or, if you are using a saline product, at least 80 billion.

I would like to comment on Dr. Shaw's remark. I think there may always be isolated lots of vaccines that are not effective. The manufacturers have no accurate means of assaying potency. By and large, if recently isolated strains are used, chances are you will get a good antigen.

DR. SHAW.—It will be interesting to know from those present how many failures have been encountered in private practice. Dr. Yeazell, how many have you seen?

DR. YEAZELL.—I have seen just two. One of these was a child of 6 years who had been immunized in infancy and had had no boosters. The second was an infant of less than a year of age who was immunized in the newborn infant nursery at Stanford.

DR. MILLER.—We had several hundred youngsters in which immunization was started in the nursery with saline-suspended material, and I feel sure that very few, if any, of these infants were protected. Both the age and the product were factors. I doubt if you can attempt immunization under one month to advantage. I do not believe that Dr. Sako is correct when he makes the statement that age does not make any difference.

DR. SHAW.—Immunity is, after all, more or less of an acquired skill. As age advances past infancy the capacity of the tissues to respond to vaccine stimulation improves. I think the point made by Dr. Miller about the use of adsorbed agents is very important. It does make a difference whether saline suspension, precipitated, or adsorbed agents are used. Is that a matter of particle size, Dr. Miller?

DR. MILLER.—I assume it is because adsorbed antigens are released more slowly and the stimulus is more prolonged.

DR. SHAW.—It does increase the particle size, however, and in general this is advantageous.

DR. MILLER.—I do not know.

DR. SHAW.—How about other failures in private practice?

DR. THOMAS CORNWALL.—I do not remember having seen any failures. Pertussis seems to be practically nonexistent in my practice.

DR. DEAMER.—I recall two, Dr. Shaw, one proved by culture. He had presumably been adequately immunized with three doses of vaccine totaling 80 billion organisms. The interval since the last injection was almost two years. The other case was a child who should have gotten three but had only two injections in the basic immunization. I can remember just the two failures.

DR. GELSTON.—I have seen only one failure of protection in which I do not recall the exact method or spacing of immunization. I do not immunize early but prefer to begin at 8 months of age.

DR. DEAMER.—What has been your experience, Dr. Shaw?

DR. SHAW.—I can recall only a single failure among those whom I have immunized and followed subsequently. This child was one whom I referred to an eastern colleague, an old friend in Boston, who was at the time opposed to the use of vaccine. He promptly wrote me to say that ironically enough the child had arrived having his first paroxysm of whooping cough.

I believe that the children who are immunized in private practice and continue under periodic observation by the pediatrician constitute a de luxe group with respect to the effectiveness of vaccination. In many respects such a group is far better protected than those who are immunized by public health agencies and similar institutions. By and large, these children are good subjects for immunization by virtue of their better general health, good nutrition, and, to some extent, less frequent opportunity for exposure. Protection is greatly augmented by the fact that contacts with the patient are also usually immunized,

so that the child profits not only from his own immunity but from the fact that he has so little opportunity for exposure to the disease. It is not necessary to carry out 100 per cent immunization in a population in order to give a high degree of protection to a community. The same thing is, of course, true of diphtheria and other forms of immunization.

As the immunization rate rises in the infant's environment, he enjoys progressively better protection from exposure. One may thus consider the advisability of deferring immunization in private practice until a time when the response is more unfailingly reliable. Some slight dangers have been pointed out by reported experience and these dangers of immunization would seem to be accentuated in early infancy.

DR. CLARK.—The two older children in the family of this infant evidently had whooping cough. They were sent home from school with this suspicion and the mother was provided with cough plates by the Board of Health in an effort to establish the diagnosis. Somewhat amusingly, she exposed the cough plates, did not return them for examination during the next forty-eight hours, and during this period there was such a profusion of bacterial growth on the plates that the mother was sure that the children had some lurid infection, perhaps bubonic plague, refused to submit the plates for examination, and returned the other children to school to spread the disease further.

DR. ALICE POTTER.—I have had no failures of immunization which I have observed in my own practice.

DR. GRACE GOEBEL.—I can recall one case, Dr. Shaw, in a 7-year-old child who was immunized in infancy and had had no intervening immunization.

DR. ANN BRADY.—I have one patient at the present time who is 9 years old who is supposed to have had initial immunization in infancy and a series of twelve booster shots given by the Navy. The diagnosis of pertussis accordingly seems as improbable as the number of booster doses but the mother insists that the child has a typical whoop. I suppose we must consider parapertussis.

DR. SHAW.—If we regard immunization as an acquired skill, a sort of activity which must be learned by the tissues; we must still remember that there are some who just cannot learn and there are some who never succeed in developing immunity.

DR. FRANZ BAUMANN.—In regard to a 4-year-old child who had whooping cough, the question came up as to whether one should administer pertussis vaccine along with passive immunization with hyperimmune serum. Is there any evidence to show that such a course affects the disease?

DR. DEAMER.—I do not know but I would be very surprised if it were not at least partially efficacious. An analogy is the proved anamnestic response of an individual previously immunized with tetanus toxoid who is given tetanus toxoid and tetanus antitoxin simultaneously.

DR. SHAW.—Do you have any comment, Dr. Miller?

DR. MILLER.—No, I am convinced that antigen *therapy* is of no value.

DR. DEAMER.—Even in the previously immunized individual?

DR. MILLER.—That would be a booster. I was referring to the use of antigen injections in the treatment of cases in noninoculated children.

DR. SHAW.—Our experience has certainly been most dismal in the use of any antigen against pertussis or the treatment of those not previously immunized. In this particular case we decided to employ a recall injection because of the previous immunization. That the child began to improve about this time probably has no critical significance.

DR. GELSTON.—I would like to know how long we should keep up booster injections, how many there should be, and at what intervals they should be given.

DR. SHAW.—My own practice is to give a booster about two years after beginning immunization at 6 months of age and to give another one at about 3½ years of age. I find a good many children come to me with instructions that they be given annual boosters. This makes the periodic visit to the doctor rather a trial. What do you think about this? We will ask our experts.

DR. MILLER.—I think you are right. A booster two years after the original course and another one at 6 years of age should be sufficient. I would be inclined to give another one when the child enters high school, having seen some cases in high school youngsters.

DR. SHAW.—Do you not think that the precipitated vaccine is better for the recall injection?

DR. MILLER.—I do not know. We have always used saline-suspended vaccine and found this satisfactory.

DR. SHAW.—The principal use which I make of triple vaccine is for recall injections because I usually divide immunization against pertussis from slightly later immunization against diphtheria and tetanus.

DR. GELSTON.—Is there any reason why rabbit serum was used for treatment in this case rather than hyperimmune human gamma globulin?

DR. SHAW.—The only reason was because we have a small supply of this product on which we are running an experimental study and we have had a very few cases on which to try it.

DR. DEAMER.—I have been very favorably impressed with the Cutter hyperimmune product, so favorably impressed with it I have never gone on to use anything else, but the total number of cases in which I have used it has been quite small. One interesting thing we might look toward in the future is the possible use of polymyxin. I know that in one case in which it was used the improvement was marked. On another it was not as dramatic.

DR. KERR.—We used aerosol streptomycin here. One could not say that there was any very definite response to this treatment or that we observed anything except the spontaneous course of the disease. The child came in completely fatigued and whooped even harder for a day or so as her hydration and strength

improved, and thereafter she began to improve rapidly and her paroxysms lessened.

DR. SHAW.—I have seen worse cases of whooping cough but never more typical ones. I wish I had a sound recording of the whoop to save me the necessity of mimicking the paroxysm for succeeding classes of medical students.

COMMUNICABLE DISEASE DEPARTMENT

Four Cases of Bacteriemia

DR. E. B. SHAW.—We now consider a group of cases in which the etiology was established by blood culture. These cases of septicemia, although bacteriemia is probably a better word, are presented especially to point out the differences in blood stream infestation due to different organisms and particularly to point out the unique problem which is presented by meningococcemia.

DR. WILLIAM J. KERR (Resident Communicable Disease Service).—The first case will be presented by Dr. Randolph.

DR. RANDOLPH.—C. G. was admitted as a private patient of Dr. Roland T. Seitz. Three days before entry she complained of pain in her right thigh which became so severe as to cause her to be unable to walk. Her temperature gradually increased and on entry was 40.0° C. Examination at entry showed tenderness and swelling over the medial upper aspect of the right thigh. There was distinct limitation of motion of the right hip joint which was believed to be more on the basis of soft tissue infection rather than intrinsic inflammation of the joint. A small, crusted abrasion above the right external malleolus was evidently the result of a preceding abrasion and when the crust was removed there was present a minute draining sinus.

The remainder of the physical examination was negative although the child appeared quite ill. The white count was 6,650, polymorphonuclears 85 per cent, of which 54 were nonsegmented polymorphonuclear cells. Blood culture taken at entry later showed hemolytic *Staphylococcus aureus* which was demonstrated to be sensitive to penicillin.

Therapy was instituted on admission on the basis of a clinical diagnosis of staphylococcus bacteriemia and the child received throughout her stay full dosage of penicillin and sulfadiazine. There was prompt improvement in her general condition with a return of her temperature to normal after five days. She was placed in Buck's traction which relieved the muscle spasm. An x-ray of the hip taken several days after admission revealed a soft tissue swelling without demonstrable evidence of bone or hip joint involvement. She was dismissed ten days later entirely well and her subsequent course was uneventful.

DR. KERR.—This was considered to be a typical case of staphylococcus bacteriemia associated with a known point of entry. I should like Dr. Seitz, who was responsible for her care in the hospital, to discuss this case.

DR. R. P. SEITZ.—There is little to say about the onset symptoms except to say that these were initially very indefinite. The original abrasion, which was

occasioned by skating, was most innocuous in appearance. The presenting symptom was fever which was at first believed to be accounted for by influenza, which was current at the time. The rising temperature during the next forty-eight hours, the appearance of general toxemia, and the signs about the right hip gradually pointed to more serious possibilities and she was admitted to the hospital with a preliminary diagnosis of osteomyelitis. Therapy was promptly instituted and the confirmatory blood culture was returned five days later at a time when her clinical progress was entirely satisfactory.

This case, especially in its fortunate outcome, demonstrates the importance of initiating therapy on the basis of a clinical diagnosis and of obtaining blood cultures for the confirmation of diagnosis before therapy is commenced. This diagnostic procedure is especially important in the cases which may require prolonged therapy or in which the response to treatment is less dramatic. Blood culture and other materials for adequate bacteriological diagnosis must be secured before chemotherapy or antibiotic therapy is instituted.

Dr. Kerr.—The second case in this series is an example of beta hemolytic streptococcus bacteriemia and it is significant that we had to go back to 1936 for a good example of this theretofore frequent syndrome. The patient, R. W., was admitted with otitis media and fever for a period of twelve days. His symptoms began with headache, fever, sore throat, and enlargement of the glands of the neck. Eight days before admission the left ear was painful and promptly spontaneously drained thick yellow pus. Six days before admission the right ear became similarly painful and developed a profuse purulent discharge. This child had had numerous preceding attacks of tonsillitis, otitis media, and cervical adenitis.

On entry the child was extremely ill, the temperature was 41.1° C., and there was a very marked pallor. The tonsils were huge, almost met in the midline, and were acutely inflamed. There was marked bilateral cervical adenopathy. Both ears showed a profuse discharge and there was tenderness over both mastoids. Apart from the general evidences of marked prostration, the remainder of the physical examination was noncontributory.

The blood count was: red blood cells, 2.6 million; white blood cells, 16,500; polymorphonuclears, 85 per cent. The urine showed occasional white blood cells and was otherwise negative. Cultures from the pharynx, from both ears, and from the blood showed beta hemolytic streptococcus.

Bilateral myringotomy was performed on the day of admission and on the fourth day thereafter a right mastoidectomy was performed. Because of the continued irregularly high fever and the profound degree of illness, the right mastoid area was re-explored on the sixteenth day of hospital stay; the right lateral sinus was exposed and was found not to be definitely thrombosed. With continued supportive therapy, including several transfusions, there was gradual improvement and he was eventually discharged well.

Dr. Gelston, who treated this patient in the hospital, will continue the discussion.

Dr. C. F. Gelston.—I am sorry to say that I have lost track of this boy since 1936, although he seemed entirely well when last seen. This case best

illustrates the difference in management of such problems only a few years ago and at the present time since the advent of various specific agents for therapy. Previously our only recourse was to surgery and such supportive therapy as transfusion, and these problems which were previously quite common have now become a rarity.

DR. SHAW.—I should like to point out that we had to go back to pre-sulfonamide days to discover, in our hospital, a good example of this form of beta hemolytic streptococcus bacteriemia originating in the throat, involving the middle ears, spreading to the mastoid cells, and frequently provoking a thrombophlebitic process which often involved the lateral sinus with the production of an extremely septic temperature pattern and the picture of profound systemic infection. We used to see numerous examples of this type of infection every winter. The treatment of these infections was fascinating and sometimes fearful before the advent of modern therapeutic agents, and the end result was certainly unpredictable. We almost never see examples of this type of disease any more. Most of these forms of disseminated infection are simply cured before they begin by the use of sulfonamides, penicillin, and other antibiotics. Some of the nose and throat men still stubbornly insist that mastoiditis is not prevented by sulfonamides and penicillin but something very strange has happened to mastoiditis and mastoidectomies in the last few years.

The next two cases are presented as a contrast to these examples of staphylococcus and streptococcus bacteriemia. Dr. Fischer.

DR. A. J. FISCHER.—This patient, L. K., was a 9-month-old white American child who was seen on the afternoon of Sept. 20, 1948, because of high fever of 40.0° C. When the child was examined by Dr. Lee Cohn he did not appear ill proportionately to the height of the fever and the physical findings were entirely negative. A tentative diagnosis of exanthem subitum was entertained. Overnight the child received symptomatic therapy and early the following morning the mother reported that the child's temperature was normal although she reported that a faint rash appeared on the hands and feet. By 10 A.M. the child's temperature had risen again to 40.0° C. and the rash had spread to become an extensive, confluent, hemorrhagic eruption. The child was promptly admitted to the hospital where he arrived in a state of complete collapse. The temperature was 41.0° C. and the pulse approximately 200, respirations 90. A confluent, hemorrhagic rash now involved most of the skin of all four extremities. The rash involved the face with occasional areas of clear skin around the bridge of the nose. Most of the trunk was spared although there were a few scattered areas of ecchymosis. The blood count showed intense hemo concentration with a hemoglobin of 122 per cent; white blood cells, 5,100; polymorphonuclears, 36 per cent. Gram-negative diplococci were visible in many areas, especially within the polymorphonuclears, on an ordinary stained blood smear.

Intensive therapy was promptly instituted on admission: Penicillin and meningococcus antitoxin were given intravenously; sodium sulfadiazine was given subcutaneously; the child received an infusion of 300 c.c. of plasma; several injections of adrenal cortical extract were administered. Despite continued intensive therapy the child expired fifteen hours after admission.

Post-mortem examination showed markedly the extensive cutaneous ecchymosis and areas of ecchymosis were encountered in many of the viscera. The brain and meninges showed remarkably little evidence of damage. The lungs showed some areas of hemorrhage and some early pneumonia, especially in the left lower lobe. The liver and kidneys were quite normal in appearance. The adrenal glands showed only a minute area of hemorrhage in the cortex, while the medulla showed no grossly apparent hemorrhages.

DR. SHAW.—Kodachrome pictures of this patient were taken at the autopsy table under adverse lighting conditions. These pictures may not be satisfactory for reproduction but are very satisfactory for projection to illustrate the distribution and characteristics of the rash. You will note that the rash almost entirely involves the extremities and the face, the body being practically spared. There are a few small petechial spots but in general the rash is occasioned by diffuse ecchymosis which lacks the characteristics of embolic origin. The character of the eruption suggests a simple leakage of the blood through damaged vessel walls and this damage, I am satisfied, is due to an intense toxemia acting upon the intima of the vessels. The whole nature of this process is different from the other bacteriemias which we have presented. Meningococcus disease originates in an obscure infection in the upper air passages, this initial infection being sufficient to provide the production of vascular toxin which damages the vessels in such a way as to permit, on the one hand, ingress to the circulation of tremendous numbers of organisms and, on the other hand, provides the mechanism whereby blood cells and organisms escape from the circulation with the production of a typical hemorrhagic rash. In such a case as this the damage is irreversible by therapy directed against the multiplication of the meningococcus. This is often referred to as the Waterhouse-Friderichsen syndrome, but this term adds little to the useful concept of the problem since it presupposes that adrenal hemorrhage is responsible for the severe shock and fulminant course. In this case and in more than one-half of our previous cases the adrenals did not show sufficient damage to constitute a primary factor in the symptomatology. It is a much more likely hypothesis that the damage throughout the body is dependent upon an extreme degree of intoxication which sometimes happens to damage the adrenals just as it does the skin and other organs. Furthermore, the intimal damage is quite distinct from the effects of bacterial or fibrin emboli encountered in other forms of bacteriemia, especially that due to the streptococcus. Pathologic studies of Benda, Gruber, Herrick, and of Pick, together with numerous other investigators, satisfactorily establishes this conclusion.

I might inject a somewhat flippant note at this point which will nevertheless illustrate the extreme importance of the time element in treatment. Some years ago Dr. Henry Kempe inoculated a chick embryo with the spinal fluid from a patient with meningococcus disease. By the next morning the embryo was simply swimming in meningococci and the fetal movements were slowing down. Four hours after inoculation 50 units of penicillin were administered into the amniotic fluid and the egg was left in the incubator, where it hatched out into a normal chick.

(The picture was shown by projection.)

The chick seemed perfectly normal up to the time when it was presented to Dr. Danno, who took it to her ranch—where the cat ate it. This illustrates the rapid response of this organism to therapy and the potentiality for recovery if therapy is administered before irreversible damage has occurred.

DR. KERR.—A final case to be presented in this series illustrates a much more benign form of this same disease. This child, D. K., a 5½-year-old white girl, was seen by Dr. Thelander on the morning of admission with a petechial rash which had been noted only two hours previously. The child had been well until a few hours previously when she developed irritability, slight fever, and headache. Physical findings were limited to a petechial rash which diffusely involved the body, including the conjunctivae and the other mucous membranes. The throat was slightly injected and there was moderate neck stiffness. The white count was 21,800, polymorphonuclears 91.5 per cent, of which 45 per cent were nonfilamented. The spinal fluid showed 9 cells of which 4 were polymorphonuclear. The spinal fluid sugar and protein were normal. No bacterial growth was ever obtained from the spinal fluid. Blood culture was drawn before treatment was begun, and was positive for meningococci several days later. The patient was placed on procaine penicillin and in six hours the temperature dropped from 40.5° C. to normal levels, and she was dismissed after an uneventful course entirely well at the end of her quarantine period.

DR. SHAW.—This child responded to treatment as promptly as our chick embryo and was almost instantly well. Although the clinical diagnosis was promptly established by the purpuric eruption, the degree of severity was incomparably less than in the previous case and it is equally unlikely that adrenal damage was a significant part of the picture. It is of great importance to recognize promptly the significance of the purpuric eruption to the diagnosis. I recently saw a child at another hospital who had had a few days of mild illness and then suddenly became very ill with the development of a diffuse purpuric rash. The suspicion of meningococcus disease had been disarmed by the finding of a normal spinal fluid. Treatment with aureomycin had been instituted on a presumptive diagnosis of rickettsial disease. When I saw him two hours later he was greatly improved but the petechial eruption was so characteristic of meningococcemia that treatment was then instituted with sulfadiazine and by the next morning he was almost entirely well. There had been so much improvement after the single dose of aureomycin that I suspect that it actually cured this patient although I do not know of its being used in meningococcus disease. The final diagnosis was uncertain for five days when the blood culture, which had been drawn prior to any treatment, was returned positive for meningococcus, further reinforcing the belief that an extensive purpuric eruption of this sort nearly always means meningococcus disease.

DR. KERR.—In analyzing our autopsy material in this hospital during the last twenty years I find that among nine cases who died less than forty-eight hours after the onset of the disease adrenal hemorrhage was grossly present in three and was microscopically present in one. Dr. Fischer's case, which showed

extremely minute hemorrhage, was included among the three showing gross hemorrhage. Thus a total of four cases out of nine showed definite adrenal hemorrhage in fatal outcome. This percentage distribution of adrenal hemorrhage agrees fairly well with some of the literature. An excellent report by Ferguson and Chapman in the *American Journal of Pathology,* July 4, 1948, describes sixteen cases of fulminating meningococcus toxemia, among which there were nine which showed adrenal hemorrhage. These authors also subscribe to the view that the term Waterhouse-Friderichsen syndrome does little to clarify the picture and believe that toxemia and not adrenal damage is responsible for the fulminant advance of symptoms.

DR. SHAW.—We have presented two cases of localized pyogenic infection due to the staphylococcus and the streptococcus which resulted in sufficient blood stream infestation for the organism to be demonstrable by blood culture. In the days prior to sulfonamide and antibiotic therapy such examples of bacteriemia were extremely common. In general, a positive throat culture in such instances is indicative of the degree of bacterial invasion. A local focus of infection immediately accessible to the blood stream readily results in bacteriemia. Favorable conditions for this event particularly occur when local infection involves a heart valve, the blood vessel wall, or tissues immediately adjacent to a rich blood supply. A local thrombophlebitic process readily leads to bacteriemia or pyemia through the dispersion of infected emboli. If neither the establishment of the original point of invasion nor the circulatory dispersion of infection is interfered with by antibiotic or chemotherapy, *secondary* foci of infection may be rapidly established and thus help to maintain blood stream infestation. Prior to modern efforts in therapy the control of these infections was dependent upon the resistance of the patient, the use of various supportive measures such as transfusion, and the final recourse to surgery in obliterating a local nidus of infection. At the present time the incidence of these bacteriemias has been greatly reduced by the effective prevention not only of the original focus of infection but also of secondary disseminating foci equally accessible to the blood stream. We have attempted to illustrate that the problem of extreme infestation in meningococcus disease represents an entirely different mechanism of blood stream invasion in which rapid production of an intensely active vascular toxin is responsible for the ingress of organisms into the blood stream to an extent not comparable to most other pyogens, the same toxic agent being responsible for the easy egress of these organisms from the blood stream into vulnerable tissues. In meningococcus disease minimal therapy applied sufficiently early may effect a rapid cure, but if treatment is delayed, sometimes for even a short period of time, irreversible damage may be produced which is incapable of response to agents inimical to the infecting organism.

Psychologic Aspects of Pediatrics

THE SUMMER CAMP

CORNELIA GOLDSMITH
NEW YORK, N. Y.

FOR children of today who live in cramped and congested large cities, in small apartments with remote and limited outdoor play space, and who attend crowded schools, a summer at a camp in the country is of increasing importance and popularity. New camps of all kinds are being established beyond the periphery of our big cities. The already existing ones are expanding their facilities to meet the growing demand. This rapid expansion of the summer camp movement applies both to the increasing numbers of children who go to summer camps and also to the broadening of the age span considered eligible for enrollment. More and more children, as well as younger and younger children, are leaving their homes during July and August each year to become "campers." It is not unusual to find camps enrolling 200, 300, or 400 children, or to find what are called "brother and sister camps" adjacent to one another under joint ownership and direction. A single day camp within the borders of New York City accommodates nearly 1,000 boys and girls from 3 to 16 years of age. Nor is it unusual to find increasing numbers of 2-, 3-, and 4-year-old children attending camps originally established for older children. These groups are commonly known as the "Midgets," the "Freshmen," or the "Tinies."

Since there are no established or generally accepted minimum standards or regulations governing camp operation except the sanitary requirements enforced by most State departments of health, anyone so inclined may set up a private camp regardless of his fitness or ability to do so. It is, therefore, important to help parents select a camp with utmost consideration as to whether or not it meets their own child's particular needs, whether or not the child is ready for such an experience, whether or not the camp, after careful investigation, is found to have a sound and constructive program, and whether it is operated under adequately qualified and responsible leadership. It can hardly be stressed too strongly that parents need help in choosing the proper camp for each and every individual youngster. Many young parents of today are refusing to send their children to camp because their own camp experience was too regimented, too ready-made, too overorganized. They had no chance to meditate or relax, to establish any real contact with country life, to use their own initiative, to step an inch off the beaten path, to move without being ordered or signalled by a whistle, a bell, or a gong. Everything they did had already been predigested by an adult and they invariably carried out someone else's plan to the exact letter. On the other hand, there is an increasing number of camps in which the campers have an opportunity to live worth-while country experiences, and where creative, competent leadership is provided.

Chief Division of Day Care and Foster Homes Bureau of Child Health, New York City Department of Health.

How, then, can parents know whether or not a particular camp is the kind they are looking for and whether it is suitable for their particular child?

CRITERIA FOR SELECTING A CAMP

1. Recognition that no two children think, feel, or behave exactly alike, even at the same age. It is necessary to be aware of and concerned with what is going on inside each child and it is necessary to treat each child as a human being and not a commodity that is being shipped away for the summer because he happens to have reached a certain age, or because it happens to suit someone's convenience, or because Daddy went off to camp at this same age. The child is the person most vitally concerned, and his attitude and his readiness should be primary factors in deciding when, whether, or where he goes to camp.

2. Proximity to home is a factor of particular importance to the younger child. Camp should be near enough so that a child under 10 or even under 12 may have several visits by his parents during the course of the camp season.

3. In terms of facilities, selection is relatively easy. Because most city homes of today have all modern conveniences, parents tend to require electricity, hot and cold showers with every bunk, et cetera. Innumerable camps do provide these conveniences. In fact, many compete with one another in building more and more luxurious and "swanky" facilities for the children, as though a camp were to be judged primarily by the number of its toilets and showers. When mere elegance in living quarters becomes a substitute for the kind of life that brings children into close contact with the out-of-doors, it is indeed a poor camp for any child. Facilities should be clean and sanitary, safe and dry, comfortable and preferably unostentatious. Children should have adequate space and adequate provision for eating, resting, sleeping, and for both active and quiet play, indoors and out. Simplicity, naturalness, usability should be the keynote rather than mere elegance, elaborateness, or impressiveness.

4. The program should accommodate itself to the interests and needs of the children themselves. City children are hungry for direct firsthand experiences with animals and plants, woods and fields, sand and earth, fire and water, fresh air and sunshine. They need, simultaneously, to exercise their hands and minds, their muscles and their creative powers of thought. Swimming, caring for pets, hiking, picnicking, making things, building things, sleeping out under the stars, walking in the rain, going barefoot, cooking over an open fire, gardening, working with tools, singing and story-telling around the campfire, fishing, frog-catching, building a dam, digging for worms, catching turtles and snakes, strolling through the woods, watching the stars or the fireflies at dusk, climbing, running, singing, dancing, dramatizing—these are important to any child. These are experiences of which most of our city children are too often deprived. For this deprivation camps can, to a certain extent, offer compensation. Programs rich in nature lore should be flexible, varied, interesting, and geared to the interests and abilities of each group of children.

5. Staff: The finest facilities in the world are of no benefit to children unless the director and the counsellors are also fine. However, their fineness must be far more than skin deep. Manners and appearance often impress par-

ents but these qualities alone are totally insufficient. Since the children are dependent upon the camp staff during their stay at camp they must be able to count on these adults fully and at all times for understanding, guidance, leadership, and protection. Each and every adult on the camp staff must be a person who has a genuine affection for children and who also likes country living and all the growing things and people about him. People who become camp directors or counsellors should have had some professional training and experience with children of the ages for whom they are responsible whether in the field of group work, camp counselling, education, or recreation. If it is important to have well-trained teachers for our schools, how much more important it is to have camp counsellors who live with our children twenty-four hours of the day and have full responsibility for their care and guidance, equally well trained and well selected! It is never sufficient to have people who say so glibly, "But I love children." The children must know that this love goes beyond words and gestures, and gives them real protection, security, and understanding. There should be a qualified physician as well as a trained nurse and a trained dietitian on the staff.

6. Equipment should be simple and sturdy. In the country children find great joy and satisfaction in working directly with raw materials and in handling essential tools. Raw materials such as clay, paint, wood, boxes, blocks, paper, sand, water, leaves, shells, etc., have infinite possibilities for their use. Tools such as hammers and saws, hoes, rakes, and trowels, shovels, wagons, wheelbarrows, buckets, looms, vise, clamps, brace and bit, etc., should be at hand to help the child to create freely in terms of his own interests and developing ideas. Equipment should be geared to the level of achievement of each age-level group, and to the skill and competence of that group. An easy, friendly framework of scheduled routines should be established which is planned and set up for the benefit of the children themselves and not actually for the mere convenience of the adults. Children do not need to be lined up, shouted at, whistled at, regimented, nor publicly humiliated at any time. Camps where this is the regular stock in trade should be shunned.

7. The intangibles, though hardest to measure, are truly the basic essentials in camp life. They exist in what we call the "atmosphere" of the camp, in the quality of the relationship between the children and the adults, as well as among the children themselves and the adults among themselves. Some conflicts and misunderstandings invariably occur in all group situations, just as they do in all family situations. What matters is how they are handled, how they are resolved, and what is the outcome. When conflicts are merely avoided and differences glibly covered over by adult tactics and not satisfactorily resolved, children never come to grips with themselves, with their own problems, or with each other. Real friendship, like all good human relationships, must have roots which must be nurtured. Even small things that go wrong must be handled in a real way, wisely and honestly, regardless of how trivial they may seem at the time. Otherwise molehills often grow to mountains and represent impenetrable barriers to growth and to good feeling. The camp staff should be sensitive to

group as well as individual problems and have skill and forthrightness in handling them.

8. The health of the children involves their physical, mental, and emotional health, if by health we mean each child's total well-being. From the physical aspect every camp, regardless of its size, should have isolation facilities with the nurse in charge. Approved first aid equipment should be available but kept out of reach of the children at all times. Every child should come to camp with the written report of a recent medical examination. Every member of the staff should have had a medical examination and chest x-ray just before coming to camp. Parents should be notified promptly whenever contagious disease develops in the camp. Good nourishing food, sleep, rest, and activity should all be appropriate, sufficient, and geared to the needs of the children themselves to prevent fatigue, strain, or overstimulation. Records of immunization and the contagious disease history should be available for every child.

9. *Additional benefits* may accrue to children in their camping experience if they have the opportunity to live in an intercultural group at camp. To enjoy living with people of different skin colors than their own, different national, social, and religious backgrounds, is an enriching experience which helps to prevent racial and religious prejudice from gaining a foothold. To know people naturally, without being made self-conscious about differences, gives children an added dimension in their living and a genuinely democratic approach to their thinking. Camps can provide such opportunities, free of rivalry, prejudice, artificial goals, or a distorted sense of human values.

DRAWBACKS TO CAMP LIFE

Now let us look briefly at the drawbacks and possible hazards to children in being sent to camps without the most careful preliminary study and selection:

1. *Overstimulation.*—Living in a group twenty-four hours a day is far more stimulating than living in a family. Children without proper guidance and controls may easily become overstimulated to the point of acute fatigue. Rather than building health, this undermines their physical and nervous structure and does them definite harm.

2. *Competition.*—Living in a group where competition is unduly stressed often creates such acute rivalry that it interferes with the development of normal friendly relations between children. Getting ahead, being best, winning the game, proving one's prowess supersede every other concern or interest and become the motivating drive, defeating all others. When the competitive element is stressed or featured, the children attain a false perspective, are determined to outdo and outdistance everyone else regardless of the effect on others, and lose the real benefits of their group experience. Such camps frequently set standards of achievement at such a high level that only the exceptional child can reach them. Consequently the majority of other children suffer frustration and a sense of defeat that leaves them with feelings of insecurity, inadequacy, inferiority, and hostility. Nevertheless, such camps continue to pride themselves on their high, unattainable standards. Many children are hurt far more than they are helped in such camps.

3. *Stereotyped Program.*—Where the program is fixed, set in advance in every detail, and every moment of each child's day is already accounted for on paper before he arrives at camp, it is obviously not geared to his needs or his interests. Such a program is mechanized and regimented and can have little real connection with, or meaning to, the children themselves. It is adult-imposed, inflexible, and essentially harmful. Children do not readily or willingly stay in such pre-ordained ruts and a considerable weight of adult control is needed to keep them there. This, too, is harmful. It develops increasing dependence rather than independence in children.

Every child's energy needs to be released naturally and constructively. He needs to express his own ideas, to explore and experiment with materials to use his inventive and creative powers, to develop initiative, judgment, skill, and confidence. To follow a fixed formula, set up in advance, makes him a mere mechanical automaton and robot. It hampers his development and stops his thinking. Children do not benefit by going to such a camp. Rather than being subjected to such harmful influence, a child should be kept at home.

4. When an insecure child or a too-young child is sent to camp before he or she is ready, great harm may be done. The child's first separation from home has dramatic, lasting, and profound meaning to him. If children are forced to go to camp, regardless of their willingness or readiness, the camp and the home are in league against them, pushing them irrevocably into a tragic and hopeless dilemma.

There are times during the growing up process when children need to spend a summer with their own parents more than they need anything else, whether or not the summer can be spent in the country. Considerate and aware parents will plan a summer around the needs of their children when this is the case. A family vacation may offer delights and reassurances that no camp can give, no matter how good.

A child gifted in any special area should not need a special camp for music or dramatics, for horseback riding or swimming, for arts and crafts or dancing. These activities should be an integral part of the program in every good camp, and every good camp should allow the special interests of children gifted in one field or another to thrive and to develop. Without being made to feel "special" these children can contribute richly to group plans and activities.

The handicapped child should also, whenever possible, be included in the regular group living of normal children. Unless the handicap is so acute as to require bed-care, or the entire attention of an adult, most average groups of normal children can absorb a not too severely handicapped child with benefit to all. To achieve this successfully it is essential that in such a group setup there is primary concern for the welfare of each individual camper, and different and conspicuous concern should not be shown exclusively for the welfare of the one child who may be handicapped.

To get sound, well-considered, professional advice regarding the selection of suitable camps to meet the differing needs of different children is difficult. Many camp counselling offices are set up by camp advertising publications, or by organized private camping groups themselves. Some are more reliable than

others. Objective, uncommercialized, professional advice in this field is greatly needed by parents. In the New York City area the Child Study Association of America has a full-time camp counsellor on its guidance staff, who gives consultant help to those parents who can come in for an interview. There is great need throughout the country for a sound, subsidized private camp advisory service.

Wherever possible, it is well to plan a year in advance as to the selection of a camp and to visit during the previous summer any camp under consideration, in order to observe it while it is in operation. This is perhaps the best way to be sure. Camp literature is only as reliable as the person who writes it. The pediatrician can help parents to analyze their motivation in sending a child to camp and the child's readiness to benefit by it, physically, mentally, and emotionally.

Comments on Current Literature

DEXTRAN AS A PLASMA SUBSTITUTE

IN A recent issue of *The Lancet* (Jan. 22, 1949) reports from Sweden[1] and Britain[2] on the use of dextran as a plasma substitute are presented. Since Bayliss[3] (1919) showed that a fluid which contained colloids having an osmotic pressure similar to that of plasma-proteins could be used as a substitute for blood, several substances, including starch, dextrin, gelatin, and gum arabic, have been used. Of these, gum arabic proved the most satisfactory. However, gum arabic was discarded because it was found to be stored in various organs and interfered with liver function. Other colloids, including pectin, polyvinyl alcohol, methyl cellulose, and polyvinyl pyrrolidone were used but with equivocal results. All of them showed storage phenomena to some extent.

In 1943, Grönwall and Ingelman[4] in Sweden suggested the use of dextran as a substitute for plasma. The material produced commercially under the name "Dextran Ph" is described by the Swedish firm, Pharmacia, as a 6 per cent solution of the polydispersoid glycose-polymer, dextran, with 0.9 per cent sodium chloride added to it. This product is virus-free, does not lead to the formation of antigens, and contains almost no nitrogen. Its threadlike molecules are electrically neutral and chemically indifferent.

In Sweden, dextran has been given to 5,000 patients, 20,000 units having been infused. It was found to be nontoxic and produced no injury to tissues either locally or systemically. Thorsén[1] has shown by careful observations that "Dextran Ph" is useful as a substitute for blood and plasma in cases where an increase in blood volume or in colloidal osmotic pressure is desired.

Bull, Ricketts, Squire and their associates[2] verified these clinical results with the Swedish product and undertook more extensive studies with a British preparation of dextran. These authors define the theoretical requirements of a plasma substitute as follows:

"*Positive Qualities:*

1. Its colloid solutes should be retained in the circulation until their place can be taken by the natural proteins. This implies that (a) the colloids should not pass readily into the tissue fluids nor be rapidly excreted by the kidney (a molecular size of at least 70,000 is, therefore, usually desirable); and (b) the colloid substance should not be rapidly metabolized or otherwise removed by the tissues.
2. The solution used for infusion should have an osmotic pressure and viscosity similar to those of plasma.
3. The composition from batch to batch should be constant, within narrow and definable limits.
4. The material should be stable during storage and preferably not require special conditions of temperature.

"*Negative Qualities:*

5. It must not be toxic, either locally or generally.
6. It must not induce fever.
7. It must not induce sensitization.
8. It must not be stored for long periods in the tissues.
9. It must not act as a diuretic. Apart from the absence of specific diuretic properties, this implies that it should not contain large amounts of solutes of low molecular weight."

Dextran is considered by this group of workers as fulfilling most of these requirements. Their experimental observations indicated lack of toxicity, pyrogenicity, and antigenicity of the product and showed its value in the restoration of blood pressure in animals deprived by bleeding of approximately one-half their blood volume.

Immediately after infusion the erythrocyte-sedimentation rate was increased, its alteration varying with the plasma-dextran level. These findings were unassociated with any adverse clinical signs. Another interesting observation concerned the fact that a raised plasma-dextran level is always associated with a lowered plasma-protein level. When the plasma-dextran level falls, the plasma protein level rises again, and in several cases studied in detail, it was evident that the total of protein plus dextran tended to remain constant.

Preliminary clinical trials with British dextran were carried out on six patients with inoperable carcinoma. Aside from transient increase in jugular venous pressure in two patients, no untoward symptoms or signs were noted. The observers concluded that British dextran was bland, pyrogen-free, and well tolerated by the recipients. Subsequent to these preliminary trials, dextran was given to twenty-nine patients undergoing more or less severe surgical operations and to two patients with burns. While death occurred in one of the cases with burns, necropsy revealed no evidence that dextran contributed to the fatal outcome.

These studies indicated that dextran is well retained in the circulation, and that it can maintain the osmotic pressure until its place is taken by plasma proteins. The importance of the molecular weight of dextran is emphasized, since dextran of lower molecular weight escaped in the urine soon after infusion. The need for a uniform preparation with a defined range of molecular size is stressed by the authors, who point out that this must be worked out before reproducible clinical effects can be expected.

The evidence presented seems to favor the use of dextran as a plasma substitute. However, a word of caution is interjected since the ultimate fate of the preparation in the body is not certain. An ideal substitute for plasma should be metabolized completely or excreted. Until these facts are established, dextran cannot be recommended unreservedly. Apart from this uncertainty, dextran appears to be free from the disadvantages of other nonprotein substitutes for plasma. The results reported in these recent studies are encouraging. The advantages of a readily available virus-free plasma or blood substitute are obvious. Should the claims of these workers be substantiated, it appears likely that hospital transfusion services may come to rely to a considerable extent on dextran for emergency cases.

RUSSELL J. BLATTNER

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Book Reviews

Child Health Services and Pediatric Education, The Commonwealth Fund, New York, N. Y., 1949, 296 pages. Price $3.50.

In the winter and spring months of 1944 a number of conversations took place among Academy members culminating in the decision that postwar planning for initiating or extending child health programs on a national or local basis could be greatly facilitated by a survey of the existing health services and facilities for children throughout the United States. Such a proposal was placed before the Academy at its national meeting in St. Louis in November, 1944, and was unanimously adopted. President Gengenbach appointed a committee of nine which subsequently selected Dr. Warren Sisson of Boston as its Chairman. Dr. John Hubbard, also of Boston, and who was just terminating his period of war service, was chosen as the Executive Director. Both the U. S. Children's Bureau and the U. S. Public Health Service readily accepted the Academy's request to assist in the study.

Thus began one of the most unique undertakings ever attempted by an independent body of physicians. That it has been pushed through on an order of magnitude and to a degree of thoroughness far beyond the vision or expectation of those who initiated the idea is a testimonial to the abilities of the Academy organization, its state chairmen, and its Study Committee, with special laurels going to the Chairman, Director, and Executive Staff. Facts about the medical facilities and services for the care of children in the United States and about the training qualifications of those who render the care have been assembled which should be of inestimable aid in planning national and state child health programs for many years to come. That the Academy intends to make full use of the data collected and processed is shown by the appointment of a continuing committee, the Committee for the Improvement of Child Health.

The study has taken approximately three years to complete and about a million dollars. Publication of the findings in a two-volume set has been completed and is available for public inspection. Volume I is a general summary of child health services and pediatric education. Detailed tables and a description of techniques considered too voluminous to be included in the first volume are available in Volume II. In addition to these two volumes at the national level, each of the states is publishing its own report, from which it is hoped will come planning at the local and state level adapted to the needs peculiar to conditions in the individual state.

That portion of Volume I dealing with child health services consists of a foreword by Dr. Sisson and of seven chapters. It summarizes the information gathered from physicians and dentists and from hospitals and community health agencies. Chapter 1 outlines the plan and method of study and describes the basis of comparisons by state, region, and by county groups. Of especial interest is the method devised to compare health services available to rural and to urban children. It was recognized that many people living in rural areas are at the same time near enough to urban centers to permit easy access to the facilities of those centers. But in rural areas far removed from urban centers services received are, for the most part, restricted to those which can be obtained locally. Hence, five groups of counties were created—greater metropolitan, lesser metropolitan, adjacent, isolated semirural, and isolated rural. Greater

metropolitan counties are those in or around the twelve major cities of the United States. There are sixty-three of these. Lesser metropolitan counties are those which include all or portions of cities of 50,000 or more inhabitants. These number 177. Counties geographically contiguous to any of the metropolitan counties are classified as adjacent even though they in themselves may be predominantly rural. It is assumed that people in these adjacent counties readily cross county lines to avail themselves of the hospital facilities and specialists' services in the urban centers. There are 668 adjacent counties. An isolated semirural county is one in which there is one or more incorporated community of 2,500 or more inhabitants, and an isolated rural county is one in which there is no incorporated community of over 2,500 inhabitants. There are 1,116 of the former type of counties and 1,052 of the latter. Together they account for more than two-thirds of the total number of counties. Thirteen million of the total of 36,000,000 children under 15 years of age in the United States as of July 1, 1945, lived in the isolated semirural and isolated rural counties.

The next six chapters which give the data, well illustrated by charts, describe health services available to these two groups of children, the 13,000,000 in the isolated counties and the 23,000,000 in the metropolitan and adjacent counties. Comparisons are made on a state, region, and county group basis. For the purposes of this review, a few of the more striking comparisons are included in the following paragraphs.

The ratio of general hospital beds in relation to children in the metropolitan and adjacent counties is 15.4 beds per 1,000 children, while in the isolated counties the ratio is 8.4 beds per 1,000 children. It is not to be assumed, of course, that 15.4 beds per 1,000 children is the optimum number of beds which should be provided per 1,000 children throughout the nation, but it is clear that the number of hospital beds for rural children is deficient by nearly 50 per cent as compared to urban children.

Of interest is the distribution of physicians on a physician-child ratio according to county groups. In 1946 there were 116,795 physicians in private practice. This is one practicing physician for each 1,200 persons or 0.8 physician per 1,000 population. Related to child population the over-all rate becomes 3.2 physicians per 1,000 children. Analyzed according to county groups, there are 4.1 physicians for each 1,000 children in the metropolitan and adjacent counties as compared to 1.8 physicians per 1,000 children in the isolated counties. Thus, the 13,000,000 children residing in the isolated areas have less than one-half as many physicians per 1,000 of child population as do the 23,000,000 children who live in or close to urban areas. This discrepancy is probably not so important so far as specialists' services are concerned, for the child in need of a specialist's services can usually be transported to the specialist or vice versa, even though the distance be considerable. It is important, however, in the case of the general practitioners, for it seems reasonable that there should be at least an equal ratio of general practitioner service available for the rural child as for the urban child. In fact, it would be logical to argue that there should be more general practitioner service in the rural area since the full burden falls on the general practitioner's shoulders alone and the distance between patients is much greater. But instead of finding more general practitioners in rural areas we find fewer. There are 3.3 general practitioners for each 1,000 children in the greater metropolitan counties but only 1.2 in the isolated rural counties.

So far as distribution of dentists is concerned the situation is even worse. The national average is 1.8 dentists per 1,000 children, with a concentration of 3.4 dentists per 1,000 children in the greater metropolitan counties but only 0.6 in the isolated rural counties.

The deficiencies which exist in isolated counties in hospital beds, physicians, and dentists are shown in another way. One-third of the total population and, because rural families tend to be larger than urban families, 37 per cent of the children live in the two groups of isolated counties. Yet only 24 per cent of the total hospital beds, 21 per cent of physicians, and 19 per cent of the dentists are available locally to this portion of the population. To equalize the deficiencies in these three categories of health facilities would require at least a 50 per cent increase in hospital beds, doubling of the present count of 19,700 general practitioners, and tripling of the present number of 12,700 dentists in these isolated counties.

To compare the distribution of health services on a regional basis the country was divided into five regions—Northeast and Central, Southeast, Southwest, Mountain and Plains, and Pacific. The group of Southeastern states contains 6,000,000 children residing in isolated counties or nearly one-half of the total number of 13,000,000. Children in the isolated counties of the Pacific and Northeast-Central regions have two or three times as many hospital beds per child as in the states which make up the Southeastern region.

One might suppose that the deficiencies in rural areas in physicians' services would be compensated for in part by an increase in such community health services as well-child conferences, school health services, public health nursing service, and the like, but such is not the case. The Academy's study has revealed that these services are deficient in the isolated areas in about the same degree as the other health services already mentioned. In the year in which the study was being made, well-child conferences were held in only one-third of the counties in the United States. Two thousand thirteen counties, or two-thirds of the total, had no well-child conference. In 1,065 counties no public health nursing service for children was available and in 1,545 counties there was no organized program of medical service in public elementary schools. Community health services of these types are concentrated in urban areas where financial support is available.

One fact which the Academy's Study has sharply pointed up is the extent to which the children of America are dependent upon the general practitioners for their medical care. Seventy-five per cent of the total child visits in one day were made by general practitioners, 11 per cent by pediatricians and 14 per cent by other specialists. When broken down into county groupings it is seen that in greater metropolitan counties the general practitioner accounts for two-thirds of the child visits in private practice; in isolated counties, 98 per cent. A thousand children residing in predominantly urban states such as Illinois or Massachusetts on an average day receive over twice as much medical care as a thousand children living in such rural states as Mississippi or Alabama. If it can be assumed that children in urban areas are not getting too much medical care, then it follows that children living in rural areas are getting less than one-half the medical care they need. There is also the quality of medical care to be considered. Hospitals in cities have better laboratory, x-ray, and other diagnostic facilities than do rural hospitals. Children in and near cities have relatively twice as much hospital care, five times as much clinic care, and nearly five times as many visits to the pediatrician, while consultation services of other specialists are far more readily available. All this adds up to the conclusion that the city child has greater opportunity for health than the country child. In fact, the infant mortality rate for the five years of 1941 to 1945 was thirty-eight for the metropolitan area and forty-seven for the isolated counties.

Clearly, the study as summarized in the report has demonstrated beyond question the maladjustment of health services for children in the United States. This should not be interpreted as taking anything away from the fine

record of progress which has been made by this country in the care of its children. *It is* a fine record and one of which every citizen in America may be justly proud. But the point is, can a still better job be done? The answer to this is a definite yes, and the study has certainly achieved its primary objective of pointing out some of the things that need to be done in order that the health of all our children may be improved still further. Perhaps a closing comment or two on this point may be permitted.

There are some 3,500 pediatricians in practice in the entire United States. Three-fourths of these live in cities of 50,000 or more population. There would seem to be no prospect whatever in the foreseeable future that the number of pediatricians will be increased sufficiently to provide pediatric care even for the children in the metropolitan areas alone, to say nothing of the rural areas although the need for more pediatricians is great. Any approach to improving the health services and facilities for all children must, therefore, be centered around the general practitioners. First of all, there needs to be more of them, and more of them in rural areas. They prefer to live in the urban areas where hospital, laboratory, x-ray, and specialist services are more readily available, and where their families can have the advantages that go with urban living.

Unquestionably, the construction of hospitals and health centers in rural areas as provided for under the Hill-Burton Act will do much to attract more general practitioners to rural areas, but the job is not one of easy solution. For unless laboratory, x-ray, and other technical personnel and facilities are provided to staff these institutions, the rural physician will still lack important tools needed for the practice of good medicine. A major share of the responsibility for the securing of adequate community health services, including physicians, nurses, and public health units, would seem to rest with the communities themselves. Initiative in this direction, if pursued with sufficient zeal, might be successful in many instances. A problem of equal, if not greater, significance so far as children are concerned to that of increasing the number of general practitioners in rural areas is the problem of increasing the pediatric training of the general practitioner. Since 75 per cent of the children of the nation are dependent upon the general practitioners for their pediatric care, it is clear that any improvement in the health of children on a nationwide scale must come about through better pediatrically trained general practitioners. Approximately one-third of the visits made by the general practitioner on an average day are made to children under 15 years of age, and yet nowhere near one-third of his undergraduate or postgraduate training is spent in pediatrics. But this leads directly to that portion of the report which deals with Pediatric Education. There needs to be added here only a word of congratulation on the excellence of the report and an expression of hope that it will find the field of usefulness which it richly deserves. L. F. HILL.

PEDIATRIC EDUCATION

In the final analysis the medical care which a child receives is dependent on the knowledge of the physician responsible for his care, and this, in large measure, depends on the physician's training. It was for this reason that a study of pediatric education became an integral and necessary part of the study of child health services. A subcommittee of pediatric teachers, with Dr. James L. Wilson as chairman, was formed to outline the study. Dr. John McK. Mitchell, the present Dean of the University of Pennsylvania Medical School, became Director of the study. In the school year 1946-1947 and the first semester of 1947-1948, he made personal visits to each of the seventy approved medical schools in the United States. A separate study of pediatrics in the Canadian medical schools, which follows a similar outline and in which Dr. Mitchell has

cooperated, is being made. Regional meetings of the heads of the pediatric departments were held prior to the visits, and thus each school was familiar with the data sought for the study.

The information developed by the study will, beyond question, have a tremendous influence on pediatric education as a whole, particularly in light of the findings of pediatric care in Part I of the study. Let us say at the start of the review of this Part that in the breadth and scope of the report, and in the vast amount of data that have been obtained and analyzed, the Director, Staff, and Committee in charge have done a magnificent job and deserve the thanks of not only medical educators, but of all those who in one way or another are interested in the better health and medical care of children.

The report on education, pages 141 to 250 of the volume, is divided into two parts, A—Undergraduate Education, which is subdivided into ten chapters, and B—Graduate Education, with five chapters. To this is added a summary, bibliography, and appendix tables. Thirteen graphs or charts are used to illustrate the material.

Chapter 9 discusses the seventy medical schools, their location and affiliations. Chapter 10 is concerned with student enrollment and admission requirements. It is estimated that in 1948, 21,878 individuals applied for the approximately 6,000 places available in the medical schools. The report calls attention to the increase in medical students admitted in 1946-1947 being 7 per cent over the admissions in the same schools in 1939-1940. The report states that under present conditions a further increase in the number of students in existing schools would jeopardize the quality of teaching in most schools, as they have expanded to the limit compatible with adequate standards of education. All but three schools in 1947 admitted women, and forty-six had a policy of accepting Negroes if properly qualified. With these two excellent summaries of medical school conditions as a background, the report turns directly to its immediate problems of pediatric education.

In Chapter 11 on Departmental Organization we learn with astonishment that in 1947 in four of the seventy medical schools, pediatrics was still a subdepartment of internal medicine—this despite the position of pediatrics in medical practice and the recommendation of the Council on Medical Education in 1935 that pediatrics should be recognized as a major clinical department. One can seriously question whether these schools should be continued on the list of approved schools.

In Chapter 12 on Budgets we reach one of the most important phases of the study. Much of this has already appeared in print in one form or another and is the basis of the movement for Federal support of pediatric education which has been the subject of controversy. The report recognizes the many difficulties in obtaining figures of departmental expenditure for comparative purposes, but even with the inaccuracies that are acknowledged, the over-all picture to the reviewer is a clear-cut presentation which may be accepted as valid. There are tremendous differences in the budgets of the pediatric departments. Thus nine schools have an income of over $100,000 per year and eleven less than $5,000. The average is approximately $44,000, but the median is $25,000. While the large budgets of some schools (the highest is between $250,000 and $300,000) are not a necessity for good pediatric teaching, budgets under $10,000 to $15,000 are beyond question totally inadequate. The variation is more striking and the comparison more to the point when consideration is made on the basis of the number of medical students in the school. In five schools it is less than $10 per student per year and in four, over $400. Twenty-five had less than $50 per student, twenty-five between $50 and $200, and twenty over $200. In forty-three schools the amount was less than $100 and in twenty-seven over $100.

In the various medical schools there are 460 pediatric staff members who give at least one-quarter of their time to teaching. About one-fifth of these derive their entire support from private practice. One-half serve on a part-time basis and receive a small, often only a token, salary which does not represent an appreciable contribution to their income. To quote directly from the report, "Great honor is due to the group of loyal and conscientious pediatricians who give so freely of their time and energy without recompense in order that medical teaching may go on. At a reasonable estimate there would be no department of pediatrics in twenty-eight schools if it were not for these physicians and the ones who receive a purely inconsequential sum." Not only is there a crisis in medical education which has been the subject of so much discussion, but financial support is obviously the crux of the situation. On careful study of the report it is easy to see why the Committee on Improvement of Child Health urged Federal aid for pediatric education. It is a method of financing medical education which is steadily gaining the support of medical educators.

The organization of the staff of pediatric departments, as discussed in Chapter 13, shows that in seven schools the pediatric staff is essentially on a full-time basis, in thirty-nine a combination of full- and part-time members, and in twenty-four the staff is entirely part-time. Of the thirty-nine schools with a combination staff, twenty-one were "essentially full-time" and thirteen "essentially part-time." In five schools no differentiation could be made. Thus the departments in twenty-eight schools may be considered on the "full-time" basis and in thirty-seven on "part-time." In thirty-one schools the head of the department is on full-time and on an average gives 60 per cent of his time to administration. The study then goes into such details as teaching hours and other activities of the staff members.

The teaching hours alloted to pediatrics in the medical school curriculum show a decided increase when compared with the hours twenty years ago. Thus in Chapter 14 we find that the average school in 1946-1947 had 286 scheduled "catalogue hours" for pediatrics. However, there were, in addition, on an average, twenty-eight "overtime hours" spent by each student. This is about 11 per cent of the instruction in the junior and senior years. This figure is of interest in the finding of Part I, in which it is disclosed that almost one-third of the average day's work of the general practitioner is with children. More and more emphasis is placed on the clinical clerkship as a method of instruction, with didactic teaching, particularly in the form of lectures, playing a smaller role in instruction. In five schools no formal lectures are given but in one it still constitutes over one-half of the instruction. The importance of outpatient teaching is stressed, together with its place in the curriculum. The final discussion is on the place of subspecialty teaching as allergy, child psychiatry, etc. The number of hours that should be allotted to pediatrics depends, of course, on the facilities available for teaching. It would be a waste of the student's time to increase hours without suitable facilities and material. This wide variation is shown by some schools allotting over 400 hours to pediatrics, and nine still under 200. Two hundred hours was the minimum suggested nearly twenty years ago as necessary for pediatrics. However, by and large, the report shows that the importance of pediatrics has steadily gained recognition in the crowded medical curriculum.

The next two chapters discuss the teaching of certain special phases of pediatrics as the newborn and premature infant, and the integration of social and environmental factors. Direct student contact with the newborn infant is a difficult technical problem. In less than one-half of the schools is opportunity provided for the student to perform physical examinations on newborn infants. In fifty-nine of the seventy schools the training of the student in the care of the newborn infant is the responsibility of the pediatric department. The opportunity for observation of the handicapped child is extremely spotty.

Chapter 17 takes up the all-important question of facilities. Hours assigned to any clinical subject are largely wasted if sufficient clinical material is not available. The average medical school has ninety-one beds directly under the control of the department, but one-half have less than 115. Many schools have, in addition, "supervisory beds" where teaching is done by members of the staff. Twenty-two schools have less than one bed per senior student while forty-eight have one or more. This does not include bassinets. Twenty schools have less than fifteen bassinets for teaching the care of the newborn infant. Facilities for teaching the communicable diseases are grossly inadequate in thirteen schools and in only thirty-four can the facilities be considered as satisfactory. Outpatient facilities which are so important for undergraduate teaching show wide variation. In thirty-two schools there are 100 or more visits annually per senior student, but two schools have less than twenty-five annually. The desirable ratio of one new and two to three old visits per student at each outpatient session is not found in many schools.

One of the most interesting discussions is the final chapter on undergraduate education which describes the rating of the pediatric instruction in the various schools on an objective basis. A rating sheet was devised by the staff and a committee of department heads which contained fifteen specific items with a numerical value assigned to each. The total value of the points amounted to 100 with a maximum possible score assigned as follows: staff 40, clinical facilities 22, content of pediatric course 27, budget 11. A second subjective rating was made on the impressions of each department based on certain intangibles as the spirit, reaction of student body to course, interest in research, etc. Such an over-all correlation was established with the purely objective rating that the subjective scoring was abandoned.

On the basis of the objective rating, twenty schools were placed in a high group, all of which had scores of 70 or more, thirty were placed in a middle group, and twenty schools with a score of 40 or less were placed in a low group. The discussion then goes on with a detailed comparison of the various items of rating in the high and low groups of schools. The high group had four times the teaching hours of the low group expressed in terms of the ratio of teaching hours to student enrollment, and far more in- and outpatient clinical facilities per student. The most striking difference is found in the budgets. The department budget for the high group averaged $90,000 and for the low $7,400. The high averaged $300 per student and the low $25. Five per cent of the whole school budget, which amounted on an average to $2,700 per student, was allotted to pediatric teaching in the high group, as contrasted with 1.1 per cent of the budget of $1,200 per student in the low scoring group of schools.

To the reviewer the conclusion is inescapable that if there is to be better pediatric teaching and training of American doctors, more money must be found for medical education, particularly for the schools in the low scoring group. This is the underlying cause of the marked differences in the extent and character of the teaching of pediatrics in our medical schools.

In Chapter 19 the report turns to the survey of graduate education in pediatrics. While the medical schools have assumed no direct responsibility for the program, a large part of the graduate instruction is in the teaching hospitals where it is carried out by members of the clinical faculty. No attempt was made to study the extent of pediatric training in 764 hospitals approved for general intern training. There are 180 hospitals approved by the Council on Medical Education and Hospitals of the A. M. A. for residencies in pediatrics, and 158 of these were visited by members of the study staff. Twelve of the 180 had not been approved at the time of the study. Ninety of the 158 hospitals were teaching hospitals definitely integrated with the medical schools, and sixty-eight are not used for undergraduate pediatric teaching. The first year of hospital

training following immediately after graduation is generally classified as "internship." There are 187 such positions of which all but five are in the teaching hospitals. A full-time house staff position the second year after completion of an internship is classified as an "assistant residency." There are 450 assistant residencies approved, of which 357 are in the teaching hospitals and ninety-three in the nonteaching group. The positions the second year of pediatric training after internship are classified as "residents." There are 206 such places available of which 129 are in the teaching hospitals and seventy-seven in the nonteaching. Thus there are a total of 843 pediatric hospital services of a term of one year available, of which 80 per cent are in the teaching hospitals. As the American Board of Pediatries requires two years of training at the residency level, the 656 assistant resident and resident positions provide for only one-half that number of individuals. Were all these approved residencies wholly satisfactory, it would seem to the reviewer that the opportunities for specialist training were adequate in number. Unfortunately, as is brought out in subsequent chapters, some residencies offer a far better experience and training than others. This coincides with the examination experience of the American Board of Pediatrics over the past fifteen years.

In the 158 hospitals there are, in addition, 253 positions of rotating internship for a shorter period, usually of from one month to six weeks, which provide some graduate pediatric teaching for approximately 2,000 recent graduates. But taken as a whole only 2,300 interns receive pediatric training in the hospitals approved for pediatric residencies, and 3,400 are without such experience. Certainly this finding raises an issue that needs considerable study and thought on the part of those concerned with pediatric education. To the reviewer it raises the question as to whether or not we have gone too far in the training of specialists in our children's hospitals at the expense of the education of the general practitioner who looks after the health of 75 per cent of the children.

Chapters 20, 21, and 22 are detailed discussions of the in- and outpatient training of the residents. Some hospitals have too few admissions per resident to give a broad experience and a few too many for proper study of the case. In some the newborn service is inadequate and in others the contagious. In seventy-seven of the hospitals there is little or no "well-child service," although in the survey of practice it was found that 54 per cent of all visits made by pediatricians in private practice are concerned with this phase of medical care.

Chapter 23 discusses the extent of ward rounds and conferences in the hospitals which form the basis of the "teaching" in graduate education and are of particular interest to the educator.

To the reviewer the survey and report on pediatric education leave certain impressions as a whole. First, the tremendous improvement in pediatric teaching which has steadily been taking place in recent years. As compared with the situation twenty years ago when the White House Conference study was made, the progress is amazing. It is obvious that there are many fine pediatric clinics in the United States today, when thirty years ago they could have been counted on the fingers of one hand. Second, where weaknesses exist the fault is chiefly one of budget limitations. Third, the thoroughness of the report and analysis of the data obtained on the survey. This, together with the fairness of interpretation and the broadness of viewpoint of those responsible, makes it a study of monumental value to those concerned with the care of children.

VEEDER.

News and Notes

Dr. Eugene Rush, chief of the pediatric service at the Mount Sinai Hospital in Philadelphia, died February 19, 1949.

The **Second Pan American Pediatrics Congress** will be held at the Hospital Infantil, Mexico City, Mexico, Nov. 2 to 5, 1949. The following plenary sessions are scheduled:

Nov. 2. Acute Diarrheas in Infancy
Hemolytic Syndromes of the Newborn

Nov. 3. Congenital Malformations of the Heart
B.C.G. Vaccination in America

Nov. 4. Pediatric Surgery
Virus Diseases in Pediatrics

Nov. 5. Child Neuropsychiatry
Pediatrics in the Field of Social Security

The following were certified by the **American Board of Pediatrics** at the examination in St. Louis, Feb. 18, 19, 20, 1949.

Dr. Eugene W. Austin, 216 S. E. Riverside Drive, Evansville, Ind.
Dr. Curtis A. Beerman, 300 Lincoln St., Johnstown, Pa.
Dr. Milton Carl Bessire, 1052 North 5th St., Abilene, Texas.
Dr. Richard Charles Brown, 113 E. Williams St., Owosso, Mich.
Dr. Joseph A. Browning, 184 Washington N. E., Warren, Ohio.
Dr. Cho Duke Choy, 920 East 59th Street, Chicago 37, Ill.
Dr. Harold S. Cole, 19 Donaldson Avenue, Rutherford, N. J.
Dr. Clyde Douglas Conrad, Medical College of South Carolina, Charleston, S. C.
Dr. James T. Cowart, Lafayette Office Building, Tampa, Fla.
Dr. Harry M. Estes, 225 Bennie Dillon Bldg., Nashville 3, Tenn.
Dr. Matthew Feldman, 120 Bogert Road, River Edge, N. J.
Dr. Paul M. S. Fischer, Pediatric Dept., Univ. Hospital, Ann Arbor, Mich.
Dr. Samuel W. Gollub, 4500 Olive St., St. Louis 8, Mo.
Dr. William Burton Greenberg, 315 60th St., West New York, N. J.
Dr. Caldwell K. Hamilton, Missouri Theater Bldg., 634 N. Grand Blvd., St. Louis 3, Mo.
Dr. Olga Romanov Hoffman, 57 Park Terrace Gardens E, New York City 34, N. Y.
Dr. S. Sprigg Jacob, 401 W. Grand River, East Lansing, Mich.
Dr. Max Kaplan, 1575 Gilpin Street, Denver 6, Colo.
Dr. Robert Emmett Keeley, 2376 E. 71st St., Chicago, Ill.
Dr. Howard L. Lange, First National Bank Bldg., Belleville, Ill.
Dr. Sidney S. Marder, 116-50 227th St., St. Albans 11, N. Y.
Dr. Beryl M. McDonald, 1102 Broadway, Rockford, Ill.
Dr. Luther L. McDougal, Jr., 705 West Main St., Tupelo, Miss.
Dr. Conn Lewis Milburn, Jr., School of Medicine, Western Reserve Univ., Cleveland, Ohio.
Dr. James Urban Morrison, Jr., 1430 Tulane Avenue, New Orleans, La.
Dr. Herbert F. Philipsborn, Jr., 706 Glencoe Road, Glencoe, Ill.
Dr. Elliott Podoll, 2114 Weber Avenue, Louisville, Ky.
Dr. Ivan J. Roggen, 716 Malzaan St., Saginaw, Mich.
Dr. Wendell Linwood Severy, 4614 Sunset Blvd., Los Angeles 27, Calif.

Dr. Vincent Arthur Spinelli, 27 Ludlow St., Yonkers, N. Y.
Dr. LeRoy J. Stephens, 3284 Ivanhoe St., St. Louis 9, Mo.
Dr. Edward Louis Strem, 711 Lowry Medical Arts Building, St. Paul 2, Minn.
Dr. John D. Stull, 106 North Silver St., Olney, Ill.
Dr. James Mack Sutton, Jr., 412 Third St., Albany, Ga.
Dr. Edward H. Townsend, Jr., 26 South Goodman St., Rochester, N. Y.
Dr. Robert Warner, 333 Linwood Avenue, Buffalo, N. Y.
Dr. Erle Ewing Wilkinson, 415 Chesterfield Avenue, Nashville, Tenn.
Dr. James N. Yamazaki, Children's Hospital, Cincinnati 29, Ohio.

The staff of the Children's Hospital in Denver, Colo., will hold a three-day summer clinic session June 30, 31, and July 1. There will be three full days of demonstrations and panel discussions. In addition to the regular pediatric and surgical staff, Dr. Mitchell Rubin of Buffalo, Dr. Wolf Zuelzer of Detroit, and Dr. Willis Potts of Chicago, will be guest speakers. Full information may be obtained from the hospital.

Dr. Louis K. Diamond of Boston, who has been acting as part-time technical director of the Red Cross Blood Program, has been given a temporary leave of absence from the Harvard Medical School and Children's Medical Center at Boston to assume the full-time position of medical director of the Red Cross program. Between January, 1948, and mid-February, 1949, the Red Cross had opened nineteen regional centers and one statewide mobile unit. By June, 1949, a total of thirty regional centers and programs are expected to be in operation.

The birth rate for 1948 was only 4 per cent under the rate for 1947, making it the second largest year in the history of the country. The 1947 rate was increased 50 per cent or more over 1940 in fifteen states, and between 40 and 50 per cent in fifteen others. Again history repeats itself with a high birth rate accompanying and following a war.

The **Second Commonwealth and Empire Health and Tuberculosis Conference** will be held in London, July 5 to 8, 1949.

Memorial Hospital Center for Cancer and Allied Diseases, New York, N. Y., has established a residency in pediatrics. The period of service is for a minimum of six months and its purpose is to train the pediatrician in the diagnosis and management of neoplastic diseases in childhood. The resident will also participate in the research program in progress at the Sloan-Kettering Institute. Three months' credit toward Pediatric Residency training requirements has been approved by the American Board of Pediatrics. For further particulars applicants may communicate with the Director, Pediatric Service, Memorial Hospital Center for Cancer and Allied Diseases, 444 East 68th Street, New York 21, N. Y.

Editor's Column

THE SURVEY OF PEDIATRIC SERVICE AND EDUCATION

AT A dinner at the Roosevelt Hotel in New York on April 2, the report of the "Study of Child Health Services and Pediatric Education in the United States" was made public. Because of its importance, it is extensively reviewed on page 518 of this issue. Since the study was undertaken and sponsored by the Academy of Pediatrics at its meeting in the fall of 1944, not only over a million dollars, but thousands of hours of the time of busy doctors have gone into the study. The survey staff worked unceasingly for over two years on compiling and analyzing data. Nothing like it has ever been done before and the pediatricians of America may look with pride on their attempt to evaluate the medical care which the children of the United States receive. Sound planning for the future depends on our knowledge of what is and what is not being done. This was the thought that led to the study. But the study is not an end in itself, it is only the current balance sheet of credits and debits. Now the real task comes of implementing the findings and recommendations into terms of definite action. The two most important conclusions on the basis of the findings of the survey are first, the need of better training in pediatrics for the general practitioner, and second, making it possible for children in isolated areas to receive medical and health care comparable to that in the larger metropolitan areas.

Our hats go off to all who are responsible for and aided in the work of the study and the report.

CANCER IN CHILDREN

IT IS rather startling to find that cancer, including leucemia, is now the second leading cause of deaths from disease in children between the ages of 1 and 14 years, and is the leading cause of deaths from disease in the 5- to 9-year age group.* In 1930 it was not even in the first ten causes. This change is due, of course, to the lowered mortality from the infectious diseases due to preventive measures and to the introduction of the sulfa drugs and antibiotics. Over 2,000 children die from cancer in the United States each year. Leucemia is the most common type of cancer, accounting for one-half of the cancer deaths in the 1- to 4-year age group, and two-fifths in the 5- to 9-year group. In the younger children, bladder and kidney cancer ranks second, and in older children brain tumor. Some of the increase in the number of reported deaths from cancer in recent years in all probability is accounted for by more accurate diagnosis. That all cancer in childhood is not hopeless was shown by Dargeon,† who reported patients living five to ten years after the beginning of treatment. As with adults, the earlier the diagnosis and starting of treatment, the more favorable the chances of survival.

*Reported in the Statistical Bulletin of the Metropolitan Life Insurance Company for January, 1949.

†Dargeon, H. W.: Cancer in Children, J. A. M. A. 136: 459, 1948.